PROPOFOL IN PAEDIATRIC ANAESTHESIA

M.D. THESIS

BY

CINDY SUI TEE AUN

M.B., B.S. (Rang), F. R. C. A.

Department of Anaesthesia and Intensive Care
Faculty of Medicine, Chinese University of Hong Kong.

April 1994

CONTENTS

SIGNED STATEMENT

I hereby declare that this thesis was written by myself and contains no material previously written or published by other persons. No part of this thesis has been submitted to a University or Institution of higher learning for a degree or diploma.

I also declare that the thesis embodies my own original and independent research and observation, except where acknowledged in the text and Appendix A.

C.S.T. Aun

29th April, 1994

ABSTRACT

ABSTRACT

Hypothesis

Propofol is a new intravenous anaesthetic agent with rapid and superior recovery characteristics when compared with thiopentone. After extensive evaluation, it now has a significant role in adult anaesthesia. It is particularly useful for day case anaesthesia and as a component of total intravenous anaesthesia. However, information in paediatric practice is limited and currently the drug is only licensed for use in patients over three years of age. The hypothesis of this thesis is that propofol is an effective anaesthetic agent for short surgical procedures in children. This thesis evaluates and compares the clinical pharmacology of propofol with that of thiopentone, the current gold standard for intravenous anaesthetic agents, in paediatric patients.

Research Model

It is well recognized that infants and children differ from adults in the way they respond to drugs. Pharmacokinetic and pharmacodynamic data are essential for understanding the age-related differences in disposition and for determining dosage regimens for newly developed drugs. The pharmacokinetic and pharmacodynamic studies in this thesis were carried out on healthy Chinese children aged between six months and 12 years old who required general anaesthesia for short elective surgical procedures. The research methods were designed to determine the pharmacokinetics of propofol in children and evaluate the clinical use of propofol during three phases of anaesthesia; induction, maintenance and recovery.

Induction of anaesthesia

Induction dose

The dose of propofol required in children was determined by a quantal dose response study. Three hundred unpremedicated healthy children were divided into three age groups: less than two years, two to five years and six to 12 years old. ED_{50} and ED_{95} for loss of eyelash reflex and acceptance of

face mask were determined using probit analysis. The ED_{50} and ED_{95} for both the end points were largest in the group less than two years old which decreased with age. ED_{95} for acceptance of face mask in the three age groups in ascending order were 2.88, 2.53 and 2.20 $mg.kg^{-1}$ respectively. The results suggested that a dose of 2.5-3.5 $mg.kg^{-1}$ is required for induction of anaesthesia in children, with the younger children needing more than the older ones. The induction dose required in children is larger than that required for adults (2-2.5 $mg.kg.^{-1}$).

Bolus dose pharmacokinetics

Age-related physiological changes in the distribution of body water, hepatic function, and renal function affect the distribution, metabolism and excretion of drugs. Bolus dose pharmacokinetic variables were determined by studying the blood concentration profile after a dose of propofol 2.5 $mg.kg^{-1}$ in 23 children between one and 12 years old. Blood samples were taken at 2, 4, 10, 15, 30, 45, 60, 120, 240, 360, 480, 720 minutes after administration of propofol. The pharmacokinetic variables were derived by both non compartmental analysis using statistical moment theory (NC) and by compartmental analysis (C). The mean central volume of distribution (V_C) was 0.66 (SD 0.23) $l.kg^{-1}$, volume of distribution at steady state (V_{SS}) 4.4 (SD1.78) $l.kg^{-1}$, clearance (Cl) 49.96 $ml.kg.^{-1}min^{-1}$(C) and 51.02 $ml.kg.^{-1}min^{-1}$ (NC), and $t_{1/2\alpha}$, $t_{1/2\beta}$, $t_{1/2\gamma}$ were 2.79, 24.72 and 216.48 minutes respectively. There was no correlation between age and the values of V_C, Vss and Cl. Protein binding in 22 children was compared with that in 11 adults and binding was similar (98.8% for children less than 3 years old, 98.6% for 3 to 12 years old, and 98.4% for adults). The volume of distribution and clearance values appeared to be larger than those in adults (V_C 0.48 $l.kg^{-1}$, Vss 3.54 $l.kg^{-1}$, and Cl 28.76 $ml.kg.^{-1}min^{-1}$) reported previously. However, caution is required in making a direct comparison in view of differences in methodology.

Induction characteristics

Haemodynamic response

Adult studies showed that propofol causes a significant decrease in arterial pressure during induction of anaesthesia. This aspect was studied in depth in children with two studies. The arterial pressure and pulse rate changes in response to different doses were studied during the dose finding

investigation. A reduction in arterial pressure of 15% after one minute and 30% after five minutes was observed. There was a 17% reduction in pulse rate. In the dose range of 1.6 to 2.6 $mg.kg^{-1}$ of propofol during the induction dose study, noninvasive arterial pressure monitoring showed that the reduction in blood pressure and heart rate was not dose related. In order to understand the mechanism of cardiovascular depression associated with propofol in children, the haemodynamic responses to intravenous propofol 2.5 $mg.kg^{-1}$ were compared with those to thiopentone 5.0 $mg.kg^{-1}$ in 41 children during induction of anaesthesia. Cardiac output was measured by the noninvasive technique of pulsed Doppler and two-dimensional echocardiography. The age factor was examined by dividing the children into two age groups. Eighteen children were less than two years and 23 were between two and 12 years old. The reduction in mean arterial pressure was significantly greater after propofol (28-31%) than after thiopentone (14-21%) ($p= 0.001$). A reduction in both cardiac index and systemic vascular resistance were found to be associated with the reduction in blood pressure. The reduction in cardiac index (10-15%) after induction was similar with the two agents. Baroreflex mediated increases in heart rate and systemic vascular resistance were less after propofol than after thiopentone. The baroreflex was more attenuated in children less than two years old than in older children.

Other effects

The incidence of apnoea observed following propofol administration was 0% to 53% in the dose range of 1.2 to 2.6 $mg.kg^{-1}$. It appeared to be dose-related. Pain on injection was observed in 0% to 45% of patients and was not dose related. Administration of lignocaine 0.2 $mg.kg^{-1}$ with propofol was effective in reducing the incidence of pain. Spontaneous involuntary movements were observed in 44-55% of children. This is higher than the incidence reported in adults (12-37%). No other adverse reaction was observed during induction.

Maintenance of anaesthesia

The use of propofol as a component of total intravenous anaesthesia was tested by evaluating propofol infusion anaesthesia in 38 children. A suitable infusion regimen was sought by testing a published algorithm for a pharmacokinetic model controlled propofol infusion. A pilot study was

carried out on 10 children aged between four and 10 years old undergoing minor surgical procedures. Anaesthesia was supplemented with nitrous oxide and oxygen with patients breathing spontaneously. The precision was 24.8% and bias -18.5%. The model was revised using an iterative linear least squares regression procedure. The revised pharmacokinetic variables were central volume of distribution (V_C) 432 $ml.kg^{-1}$, k_{10} 0.0967 min^{-1}, k_{12} 0.1413 min^{-1}, k_{13} 0.0392 min^{-1}, k_{21} 0.1092 min^{-1}, and k_{31} 0.0049 min^{-1}. This model was tested in another 20 children. Analgesia was provided by regional block. The precision was 21.5% and bias improved to -0.1%. The mean blood concentration required to maintain anaesthesia was 6.6 $\mu g.ml^{-1}$ (range 3.0-11.0 $\mu g.ml^{-1}$). The revised central volume was found to be 25% larger than the original data (343 $ml.kg^{-1}$). This suggested that the children studied required a higher infusion rate to maintain a similar level of anaesthesia than previously reported data in children. This pharmacokinetic model infusion was used to complete the study in a total of 38 patients. The induction dose required was 3.5 $mg.kg^{-1}$ and the mean infusion dose was 27.3 $mg.kg.^{-1}h.^{-1}$ (range 7.6 to 44.5 $mg.kg.^{-1}h^{-1}$). Anaesthesia and recovery characteristics using propofol infusion were compared with three other methods of anaesthesia: 1) propofol induction or 2) thiopentone induction or 3) halothane induction, all followed by halothane, nitrous oxide and oxygen maintenance. Apnoea was more frequent, and the incidence of involuntary movements was higher in children using propofol infusion.

Recovery

One hundred and sixty three children were selected in the recovery study. The speed and quality of recovery following propofol was evaluated using the Steward scoring system, the time to open eyes on command and the time to orientation. Psychomotor testing was included to assess the recovery of coordination ability. Recovery was slowest with propofol infusion, 39.8 (SD 12.9) min to open eyes on command. The recovery was significantly faster with the other three techniques, 21.9 (SD 9.9) min in the propofol bolus group, 23.4 (SD 11.3) min in the thiopentone bolus group and 20.1 (SD 8.9) min in the halothane group ($p= 0.0001$). There was no difference between these three methods. However, a lower incidence of vomiting was observed in children who had had propofol for anaesthesia. The slower recovery following propofol infusion was probably related to the high infusion rates

required and the large difference between the blood concentration required for anaesthesia and that at which waking occurred.

Conclusion

The studies in this thesis upheld the hypothesis that propofol is an effective induction agent. Side effects were comparable with other anaesthetic agents in use in paediatric anaesthesia. However, propofol by infusion to induce and maintain anaesthesia supplemented with nitrous oxide and regional block was unsatisfactory in the local Chinese paediatric population. Modification of the infusion and anaesthetic technique, and further evaluation is necessary before the place of propofol infusion in paediatric anaesthesia may be determined.

LIST OF TABLES

Chapter 7

Chapter 8

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAG	$\alpha_1$acid glycoprotein
AFM	Acceptance of face mask
ANOVA	Analysis of variance
ASA	American Society of Anaesthetists
AUC	Area under concentration/time curve
AUMC	Area under the concentration-time moment curve
BSA	Body surface area
C	Compartmental analysis
CI	Cardiac index
CI	Confidence interval
Cl	Clearance
CNS	Central nervous system
CO	Cardiac output
CSF	Cerebrospinal fluid
DAP	Diastolic arterial pressure
ECF	Extracellular fluid
ED_{50}	Effective dose in 50% of patients
ED_{95}	Effective dose in 95% of patients
EMLA	Eutectic mixture of local anaesthetics
GABA	γ-aminobutyric acid
h	Hours
HPLC	High performance liquid chromatography
HR	Heart rate
ICF	Intracellular fluid
iv	Intravenous
kg	Kilograms
l	Litres

LER	Loss of eyelash reflex
mg	Milligram
min	Minutes
MRT	Mean residence time
n	number
NC	Noncompartmental analysis
SAP	Systolic arterial pressure
SD	Standard deviation
SEM	Standard error of mean
SV	Stroke volume
SVI	Stroke volume index
SVR	Systemic vascular resistance
$t_{1/2\alpha}$	Rapid-distribution half life of a drug
$t_{1/2\beta}$	Slow-distribution half life of a drug
$t_{1/2\gamma}$	Elimination half-life of a drug
TBW	Total body water
V_c	Volume of central compartment
V_{ss}	Apparent volume of distribution at steady state
V_z	Volume of distribution during the terminal phase
yr	Year
µg	Micrograms
k_{10}	Elimination constant
k_{12}	Rate constant for transfer from first compartment to second compartment
k_{13}	Rate constant for transfer from first compartment to third compartment
k_{21}	Rate constant for transfer from second compartment to first compartment

k_{31}	Rate constant for transfer from third compartment to first compartment

PUBLICATIONS AND PRESENTATIONS RESULTING FROM THE WORK OF THE THESIS

Publications

Aun CST, Short SM, Leung DHY, Oh TE. Induction dose-response of propofol in unpremedicated children. *British Journal of Anaesthesia* 1992; **68**: 64-67.

Short SM, Aun CST. Haemodynamic effects of propofol in children. *Anaesthesia* 1991; **46**: 783-785

Aun CST, Sung RYT, O'Meara ME, Short TG, Oh TE. Cardiovascular effects of iv induction in children: comparison between propofol and thiopentone. *British Journal of Anaesthesia* 1993; **70**: 647-653.

Short TG, Aun CST, Tan P, Wong J, Tam YH, Oh TE. A prospective evaluation of pharmacokinetic model controlled infusion of propofol in paediatric patients. *British Journal of Anaesthesia* 1994; **72**: 302-306.

Aun CST, Short TG, O'Meara ME, Leung DHY, Oh TE. Recovery after propofol infusion anaesthesia in children: comparison with propofol, thiopentone or halothane induction followed by halothane maintenance. *British Journal of Anaesthesia* 1994; **72**: 554-558.

Presentations

Aun CST, Short SM, Leung DHY, Oh TE. The induction dose-response of propofol in children. Joint meeting of the meeting of the Association of Paediatric Anaesthetists of the Great Britain and Ireland, and ADARPEF and SIK in Basel, Switzerland. 19-21 September 1991.

Aun CST, Short TG, O'Meara ME, Leung DHY, Oh TE. Recovery in children after anaesthesia: A comparison of propofol, thiopentone and halothane. 3rd European Congress of Paediatric Anaesthesia in Liverpool, UK. 2-4 September 1993.

Short TG, Aun CST, Tan P, Wong J, Tam YH, Oh TE. A prospective evaluation of pharmacokinetic model controlled infusion of propofol in paediatric patients. 3rd European Congress of Paediatric Anaesthesia in Liverpool, UK. 2-4 September 1993.

SECTION I
INTRODUCTION

CHAPTER 1

Introduction

HYPOTHESIS AND OBJECTIVE

Propofol (2,6 diisopropylphenol), was introduced to clinical anaesthesia in 1984 with a new emulsion formulation [Cummings *et al*, 1984], and it has been extensively evaluated and used in adult patients [Bevan, 1993]. It has been shown to be a suitable alternative to thiopentone or methohexitone [Mackenzie and Grant, 1985a; 1985b; Valanne and Korttila, 1985; Walmsley, McLeod B, and Ponte J, 1985; McCollum and Dundee, 1986; O'Toole *et al*, 1987; Logan *et al*, 1987; Heath *et al*, 1988]. It is particularly useful for outpatient anaesthesia, since it provides superior operating conditions to methohexitone, a more rapid recovery, and a lower incidence of nausea and vomiting in the postoperative period [Stark *et al*, 1985; Heath *et al*, 1988; McCollum, Milligan and Dundee, 1988]. However, experience and research with propofol in children is still limited, and currently the drug is only licensed for use in children over three years of age.

The objective of this thesis was to evaluate the use of propofol, in paediatric anaesthesia, the hypothesis being that propofol is an effective anaesthetic agent for induction and maintenance of anaesthesia for short surgical procedures in children.

REVIEW OF LITERATURE

PAEDIATRIC ANAESTHESIA

Evolution and development

In the early part of this century, anaesthesia for children was administered by those few physician anaesthetists who had developed the special interest and skills needed for infants and children. It was a simple but hazardous "rag and bottle" type anaesthesia used mainly to control pain and movement [Smith, 1991]. After the second world war (1939-1945), there was a burst of activity in paediatric surgery. This brought a demand for improvement in the anaesthetic management of infants and children. It evolved more as an art than a science. However since the 1960s, there has been an explosion of knowledge of developmental physiology and pharmacology. This, together with the dramatic technological advancement in perioperative monitoring, has changed considerably the concepts and techniques of paediatric anaesthesia management.

Significant recent advances in paediatric anaesthesia include perioperative monitoring standards, the provision of intraoperative and postoperative analgesia, the rediscovery of regional anaesthesia in infants and children, the use of newer intravenous anaesthetics, synthetic narcotics and shorter acting muscle relaxants in both routine and complicated cases, day case anaesthesia, and the presence of parents during the induction of anaesthesia.

Paediatric pharmacology research

It is now well recognized that infants and children differ from adults in the way they respond to drugs. The extent of this difference was not appreciated until the 1960s. Technical difficulties and ethical issues were the major obstacles to paediatric research. The development of sensitive new techniques in assaying drugs and their metabolites, and the advances in computing technology have contributed to this dramatic development in paediatric pharmacology [Cannon, 1987]. In the United States, the Food and Drug Administration has established a policy requiring that new drugs likely to be widely used in infants and children must be thoroughly evaluated before approval may be given for marketing. However there is still a dilemma in carrying out clinical investigations in children because of the potential conflict between the ethical and scientific requirements in paediatric research. This trend is reflected by the fact only about 25% of all drugs currently available on the market in North America have undergone adequate paediatric evaluation to be considered safe and effective [Radde and MacLeod, 1993d].

Developmental pharmacology

Growth and maturation take place during the childhood period, changing the physiological factors involved in the uptake, distribution, metabolism, and excretion of drugs.

The effects of intravenous drugs depend principally on the physiological and pharmacological processes that distribute the drugs and eliminate them from the body. A number of factors that influence the distribution of drugs are age-dependent. Most notably are the composition and size of "body compartments", protein binding characteristics,

haemodynamic factors such as cardiac output and regional blood flow and membrane permeability [Besunder, Reed and Blumer, 1988a; 1988b; Radde, 1993b]. The changes in the size of various fluid compartments with growth have been well studied by Friis-Hansen [1961, 1971] and Widdowson [1974]. The body compositions at different ages are shown in Table 1.1.

TABLE 1.1. The proportions of body compositions (in % of body weight) and tissue blood flow (in % of cardiac output is shown in parenthesis).

	Newborn		Infant	Adult
	Premature	Full term	1 yr	
Total body water	83	73	60	60
Extracellular fluid	62	44	27	20
Intracellular fluid	25	33	43	40
muscle mass	15	20		50
Fat	3	12 (5)	30	15-30 (5.6)
Brain		12 (34)		2 (14.3)
Liver		5 (25)		2 (28.6)
Kidney		1 (18)		0.5 (25.7)

(From Cook and Davies 1990, data from Friis-Hansen, 1971 and Widdowson, 1974).

Body Composition

In the newborn and young infant, the total body water content (TBW) is larger (about 80% of body weight) compared with the adult (60%). The ratio of extracellular to intracellular water is higher than the proportion in adults (45: 35 vs 20: 40). The TBW, after a dramatic reduction of about 10% during the first few days after birth, decreases gradually. By one year of age, TBW has fallen to adult proportions. From this point, there is a linear relationship between TBW and lean body mass until old age. These changes in TBW are of particular relevance to water-soluble drugs. The reduction in extracellular

fluid (ECF) is more than the reduction in TBW, because of the increase in intracellular fluid (ICF). After the neonatal period, the ICF increases from approximately 33% to around the adult value of 40% of total body weight by three months postnatal age and remains steady till adulthood. The ECF volume is reduced to about 25% by one year of age, and 20% at puberty. The changes after one year are gradual. Ionized drugs tend to be confined to the extracellular compartment, so that changes in the relative sizes of the extracellular and intracellular compartments during growth will influence the effective concentration of ionized drugs.

The fat store is relatively low at birth (12% of body weight) and increases markedly during the first year of life [Friis-Hansen, 1971], but the premature infant is practically devoid of fat (3% of body weight). The small amount of fatty tissue reduces the volume of distribution of lipophylic drugs. Until recently, the measurement of the adipose tissue mass and its development has been difficult. Earlier method used radioisotopes and therefore was unsuitable for children. More recent techniques have included absorption and desorption of nonradioactive xenon [Mettau *et al,* 1977] and measurement of skin fold thickness [Durnin and Rahaman, 1967; Brook, 1971]. The adipose tissue changes in size with the various stages of development. From 1% of total body mass at 29 weeks of gestation to 10-15% at birth, it increases to approximately 15-30% by one year of age. With walking, the muscle mass develops and the adipose tissue decreases somewhat between one to two years of age until six years, before rising again at adolescence. These changes affect the distribution of lipid-soluble drugs.

Protein binding

Plasma protein binding of drugs influences drug distribution and elimination. It depends on the amount of binding proteins available, the affinity constant of the protein for the drug, and the presence of

pathophysiological conditions or endogenous substances (such as increased free fatty acids, bilirubin, urea) that may alter the drug protein binding interaction. The major proteins responsible for drug binding in plasma are albumin, α_1-acid glycoprotein (AAG) and the lipoproteins. Most of the acidic drugs are bound to albumin, whereas basic drugs are bound to lipoproteins, α_1-acid glycoprotein and β globulins. The newborn infant has a lower concentration of total protein, albumin and globulin than the adult [Boréus 1982a; Kingston *et al*, 1990]. The affinity of these proteins for drugs may also be lower than in adults [Kurz, Michels and Stickel, 1977; Wood, 1986]. As a result, protein binding is generally lower in young children than in adults. The increased free fatty acids and bilirubin in the newborn infant may significantly alter the drug binding to protein by competing with the drug for the binding sites. Hence the relationships between drug protein-binding, free drug and the resultant drug concentration can be very complicated.

Tissue blood flow

Blood flow to various tissues is one of the factors which influence drug distribution in the body. The information on haemodynamic changes during human development has been largely extrapolated from animal data [Radde, 1993b].

Following the precipitous changes of the transitional circulation at birth, the cardiac output is high in the neonates (150-200 $ml.kg^{-1}.min^{-1}$) during the first month of life [Hatch and Sumner, 1986], gradually decreasing to approximately 100 $ml.kg^{-1}.min^{-1}$ at adolescence [Robinson, 1983]. The high cardiac output during this period contributes to rapid delivery of drugs to the site of action. Heart rate decreases substantially during the first few months of life and then more gradually until adulthood with an accompanying increase in systemic vascular resistance (SVR). The SVR,

which is 800-1200 dyne.s.cm^{-5} per square metre at birth, increases to 1600 dyne.s.cm^{-5} per square metre at 12-18 months after birth [Schieber, 1990]. The arterial pressure also gradually rises towards the adult level.

Metabolic capacity

Metabolism and excretion constitute the body's mechanism for eliminating drugs. The liver is the principal organ of drug metabolism, although extrahepatic sites have been shown to be capable of biotransforming certain drugs [Juchau and Pedersen, 1973; Bakhle, 1990]. The liver mass is relatively larger in infants (4% of total body weight vs 2% in adults) providing a theoretically larger surface area for drug metabolism (Table 1.1). However, the capacity for drug metabolism is low at birth. Newborn infants are capable of performing several steps of oxidative biotransformation, but glucuronide conjugations are less effective [Boréus, 1982b]. Cytochrome P450 and nicotine adenine diphosphate hydrogenase (NADPH)-cytochrome-c-reductase occurred at about half of the adult activity [Aranda *et al*, 1974]. Alternative pathways of metabolism of certain drugs have been demonstrated in neonates [Sereni, Morselli, and Pardi, 1973; Boréus, Jalling, and Källberg, 1978; Choonara *et al*, 1990]. After birth, there is a dramatic increase in efficiency of the drug metabolising system, mainly phase I reactions. The drug disposition rate may then increase from one fifth of the adult capacity to five times faster than in adults [Morselli, Franco-Morselli, and Bossi, 1980]. This rapid elimination of drugs in children three months to three years of age gradually decreases to that of adults at puberty [Morselli, Franco-Morselli, and Bossi, 1980].

Renal function

Most drugs and their metabolites are excreted by the kidney. Both glomerular filtration and tubular function are immature in the newborn.

Elimination by other routes (bile, lungs, sweat glands, faeces) is less substantial.

Newborn kidneys contain essentially the same total number of nephrons as in adulthood. However, both glomeruli and tubules are smaller and in variable stages of morphological development. The glomerular filtration capacity is low in newborns, and increases progressively due to an increase in renal perfusion and a decrease in renal vascular resistance [Hook and Hewitt, 1977]. The glomerular filtration rate which is 30-50% of normal adult values at birth, approaches adult values by about six months of age [Boréus, 1982c]. The tubular secretary function matures at a slower rate than that of glomerular filtration [Boréus, 1982c]. Furthermore, maturation of renal function during infancy and childhood affects various drugs differently, depending on the mode of drug handling by the kidney.

Blood brain barrier

A lower efficiency of the blood brain barrier has been postulated in the newborn infant from two observations. Firstly, newborn infants have a higher concentration of protein in the CSF than adults [Adinolfi *et al*, 1976]. Secondly, animal experiments have shown that substances such as narcotics and dye penetrate into the CNS of the foetus and newborn more easily than in the adult animals [Kupferberg and Way, 1963]. However, research involving microscopic studies of the junctions between the endothelial and epithelial cells has been inconclusive [Saunders, 1977].

INTRAVENOUS ANAESTHESIA IN PAEDIATRICS.

For induction of anaesthesia in children, an inhalational method is usually used because it is rapid, relatively safe, and it avoids injections. However there are instances in which an intravenous induction of anaesthesia is the method of choice such as for rapid sequence induction. Furthermore, some children find the face mask frightening, and the smell unpleasant. It may then be kinder to use an intravenous method using a small needle than it is to hold the child down and put a mask over the face of the struggling child. The availability of local anaesthetic cream (EMLA® Astra Pharmaceuticals, Sweden) has made the intravenous injection less painful. EMLA is a eutectic mixture of lignocaine 25 $mg.g^{-1}$ and prilocaine 25 $mg.g^{-1}$ that can produce surface anaesthesia when applied to the skin 1-1.5 hours before the intravenous injection. In routine cases, intravenous induction is rapid and pleasant provided the anaesthetist is adept at the venepuncture of small veins. Anaesthetists, including trainees working full time in paediatric anaesthesia are usually quite experienced in venepuncture in small children [Brown, 1992].

THIOPENTONE

Thiopentone is an ultrashort acting barbiturate that produces sedation within one minute after intravenous administration. It was introduced in 1934 [Lundy, 1935] and remains the most popular intravenous agent in children. It is the standard against which all other intravenous agents are compared.

Pharmacokinetic profile

Thiopentone has a pKa of 7.6, and therefore changes in blood pH can lead to significant changes in the degree of ionization of the drug. It is 60% unionized at normal physiological pH. Like adults, children (five months to 13 years of age), have approximately 87% of thiopentone reversibly bound to plasma albumin [Sorbo, Hudson, and Loomis, 1984]. The plasma concentration time curve after a bolus dose of thiopentone best fits a three-compartment model. The distribution kinetics (rapid distribution half-life of 6.3 minutes and slow distribution of 43 minutes), volume of distribution at steady state V_{SS} (2.1 $l.kg^{-1}$) and volume of central distribution V_C (0.4 $l.kg^{-1}$) are not significantly different from those in adults. However, the elimination half-life is one half, the clearance (6.6 $ml.kg^{-1}.min^{-1}$) is double that of adult. Thiopentone has a low hepatic extraction ratio (0.1-0.16) [Gepts and Camu, 1991] indicating that the increased clearance in children is due either to an increase in hepatic microsomal-enzyme activity or a relatively larger hepatic mass in children. The clinical implication is that children may recover slightly faster than adults after thiopentone administration.

The main metabolic pathway of metabolism is by oxidation resulting in the production of thiopentone carboxylic acid, which is pharmacologically inactive. A small proportion is by desulphuration to pentobarbitone which is further metabolised to inactive products. The high lipid-solubility of

thiopentone results in extensive renal tubular reabsorption, and therefore minimal renal elimination of the unchanged drug. The contribution of metabolism to the recovery from thiopentone's anaesthetic effects has been recently re-examined by a pharmacokinetic characterisation of the distribution and elimination phases. This study confirms that the decline of thiopentone concentration in the brain and recovery during the first 15 minutes after a single intravenous dose results primarily from redistribution of the drug to muscle and fat tissues [Burch and Stanski, 1983]. The residual concentrations contribute to the long-lasting impairment in psychomotor skills after thiopentone [Korttila *et al*, 1975].

Pharmacodynamic profile

Thiopentone causes hypnosis within one arm-brain circulation time. A larger dose is required for induction of anaesthesia in children, 5 - 6 $mg.kg^{-1}$ for older children [Coté *et al*, 1981] and 7 - 8 $mg.kg^{-1}$ in infants [Jonmarker *et al*, 1987]. Neonates need less [Westrin, Jonmarker, and Werner, 1989], and should not exceed 2 - 4 $mg.kg^{-1}$ [Booker, 1989]. The difference in requirements in infants is probably pharmacokinetic and pharmacodynamic related [Jonmarker *et al*, 1987]. The desirable features of thiopentone include rapid onset, smoothness of action, ease of use, water solubility, painless on injection, and excitatory effects are uncommon. However, it has a number of shortcomings; its elimination is slow resulting in a slower recovery from anaesthesia and it is cumulative on repeated administration, it causes tissue irritation when injected extravascularly, and it may cause exacerbation of acute porphyria.

PROPOFOL

History

Propofol is an intravenous agent, synthesized in the laboratories of ICI Pharmaceuticals in Macclesfield, United Kingdom. The research started in 1973 with the aim of developing an agent that can produce rapid induction and recovery through rapid metabolism. The investigators also wanted an agent that could be used for both induction and maintenance of anaesthesia without producing side-effects. A number of substituted phenols that had hypnotic properties were investigated and propofol was found to be the agent with most potential. Unfortunately these phenolic substitutes are insoluble in water and therefore had to be dissolved in an organic solvent. The original solvent used for propofol was 16% Cremophor EL which was also used for Althesin (Glaxo). This was later withdrawn because of anaphylactic reactions associated with Cremophor EL. The Cremophor formulation of propofol was introduced for clinical trials in 1977 [Kay and Rolly, 1977]. However concern over the association of Cremophor containing compounds with anaphylactic reactions [Clarke *et al*, 1975; Evans and Keogh, 1977; Glen et *al*, 1979] together with high incidence of pain on injection in the early clinical studies [Major et *al*, 1981; Briggs *et al*, 1981] had led to the termination of clinical trials with this formulation in the late 1982. The drug after reformulated in an egg-oil-glycerol emulsion as a 1% solution, was available for clinical trial in 1983 [Glen and Hunter, 1984]. Propofol was approved for general use in the United Kingdom in 1986.

Chemistry

Propofol is one of a series of alkyl phenols with a molecular structure as shown in Figure 1.1. Substitution at the ortho position of the parent compound, phenol, induces steric hindrance in the adjacent hydroxyl group, modifying the hydrogen bond donor-acceptance properties. This change in structure attenuates the protein denaturing effect and confers anaesthetic activity. Optimal anaesthetic activity is obtained by substitution at the 2 and 6 positions with secondary alkyl groups so that there are a total of six to eight carbon atoms in the substituent chains [James and Glen, 1980]. It has a molecular weight of 178 daltons. Propofol is a weak organic acid with a pKa of 11, and at pH of 7.4, it is almost entirely unionised. It has a very high lipophilicity with an octanol/water partition coefficient of 3.7 [Skues and Prys-Roberts, 1989].

The commercial preparation Diprivan (ICI Pharmaceuticals) consists of propofol 1% w/v in an oil in water emulsion which containing 2.25% glycerol for isotonicity, 10% soybean oil and 1.2% purified egg phosphatide.

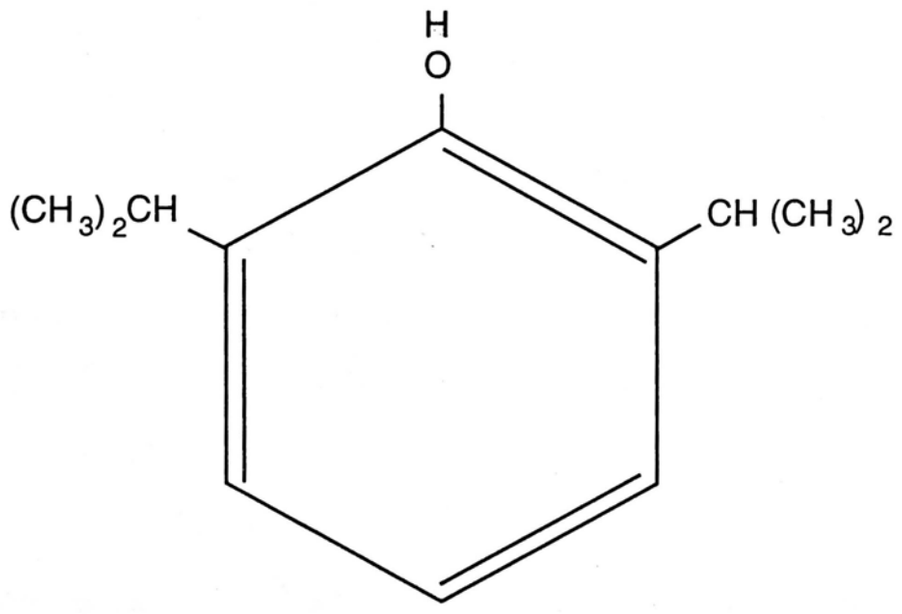


FIGURE 1.1. Structural formula of propofol

Propofol in Adult Anaesthesia

Pharmacokinetics profile

Bolus dose studies

The pharmacokinetic profile of propofol after a single i.v. dose, is usually described by a three-compartment model [Cockshott, 1985; Cockshott *et al*, 1987a; Kay *et al*, 1986; Kirkpatrick *et al*, 1988]. The three exponential functions have been interpreted as (1) a fast distribution from blood to well perfused tissues, (2) a rapid metabolic clearance from blood, and (3) a slow return of propofol from a poorly perfused deep compartment into blood. Some studies proposed a two compartmental model [Adam *et al*, 1983; Schüttler, Stoeckel and Schwilden, 1985; Simons *et al*, 1988]. The difference is probably related to the sampling method.

The major differences in propofol kinetics from those of other i.v. agents are the very high clearance values (23.2 - 29.0 $ml.kg^{-1}.min^{-1}$), exceeding the estimated hepatic blood flow (21 $ml.kg.^{-1}min^{-1}$) [Gepts and Camu, 1991], and a large apparent volume of distribution, two to three times as large as the volume of distribution at steady state, resulting in a very long terminal half-life (about 4-11 hours). This long terminal half-life indicates that propofol might accumulate when it is administered by either repeated bolus injection or prolonged infusion for maintenance of anaesthesia. Propofol in the concentration range of 0.1-20 $\mu g.ml^{-1}$ is extensively bound to plasma protein (97-99%) mainly albumin, and this is similar in both young and elderly patients. This high protein binding does not seem to restrict the extensive tissue distribution. There is a larger interindividual variation in the kinetic parameters [Kanto and Gepts, 1989] which partly explains the variations in responses observed in clinical studies.

The initial volume of distribution is smaller and the total body clearance is lower in the elderly [Kirkpatrick *et al*, 1988]. This is consistent with the reduction in the volume of highly perfused tissues, lower cardiac output [Leithe *et al*, 1984], and the age-related decline in hepatic blood flow and metabolic capacity [Hull, 1991].

Infusion pharmacokinetics

Propofol is currently the hypnotic agent of choice for maintaining anaesthesia or sedation by intravenous infusion. During constant rate infusions, the concentrations at steady-state are proportional to the infusion rate, indicating linearity of the disposition kinetics within the dose range of 3-9 $mg.kg.^{-1}h^{-1}$ [Gepts *et al*, 1987; Cockshott *et al*, 1990]. Pharmacokinetic studies have been performed in volunteers [Schüttler, Stoeckel and Schwilden, 1985], in anaesthesia [Cockshott *et al*, 1987b; Cockshott *et al*, 1990; Gepts *et al*, 1987; Shafer A *et al*, 1988; Gin *et al*, 1991] and intensive care [Albanese *et al*, 1990]. The infusion pharmacokinetic profile is fairly similar to those after a bolus injection [Cockshott *et al*, 1987b]. Both two and three compartment open-models with central elimination have been used to describe the concentration-time relationship. The pharmacokinetic variables in infusion were, in general, within the same ranges as after bolus injection, and demonstrate a large interindividual variability, especially with regard to the volumes of distribution and the elimination half-life. The apparent volume of distribution (Vd) is two to three times the corresponding volume of distribution at steady state (V_{SS}) resulting in very long terminal half-lives [Gepts and Camu 1991]. The rate constants for transfer from the third compartment (k_{31}) were only a small fraction of the values for elimination constant (k_{10}), suggesting that a small proportion of the dose stays in the tissues and is slowly eliminated.

Metabolism and excretion of propofol

Elimination of propofol is mainly through metabolism in the liver. However the existence of extrahepatic metabolism has been suggested during anhepatic phase of liver transplant [Veroli *et al,* 1992]. A disposition study using subanaesthetic dose of ^{14}C-propofol in volunteers [Simons *et al,* 1988] showed that propofol was eliminated by metabolism to water soluble conjugates of the parent compound and its ring-hydroxylated derivatives. Excretion was predominantly renal (88%). The four major urinary metabolites identified were propofol glucuronide (53%), 1-(2,6- diisopropyl-1,4-quinol) glucuronide (18%), 4-(2,6 diisopropyl-1,4-quinol) glucuronide (13%), and 4-(2,6 -diisopropyl-1,4 quinol) sulphate (9%). Less than 0.3% was found to be excreted as unchanged propofol.

Pharmacodynamic profile

Mechanism of action

Electrophysiological and biochemical studies have shown that propofol, similar to other general anaesthetics, facilitates the interaction of γ – aminobutyric acid (GABA) with its specific receptor. This in turn causes potentiation of GABA-mediated chloride conductance, leading to neuronal hyperpolarisation and inhibition of subsequent depolarisation (Figure 1.2) [Collins, 1988, Concas *et al,* 1991]. Recent work by Hara, Kai and Ikemoto [1993] has found that propofol directly activates the $GABA_A$ receptor-chloride ionophore complex and evokes a chloride current with suppression of the neuronal excitability of the central nervous system. $GABA_A$ receptor-chloride ionophore complex has been shown to be a hetero-oligomer consisting of five polypeptide subunits forming binding sites for GABA, barbiturates and benzodiazepines and chloride channel [Olsen and Tobin,

1990]. The receptor site of propofol is believed to be different from that of benzodiazepines, barbiturates and GABA. Hara and colleagues [1993] have also found that high concentrations of propofol desensitise the $GABA_A$ receptor, which may result in suppression of the $GABA_A$ system. This may be the cause for the excitatory side-effects observed during propofol anaesthesia.

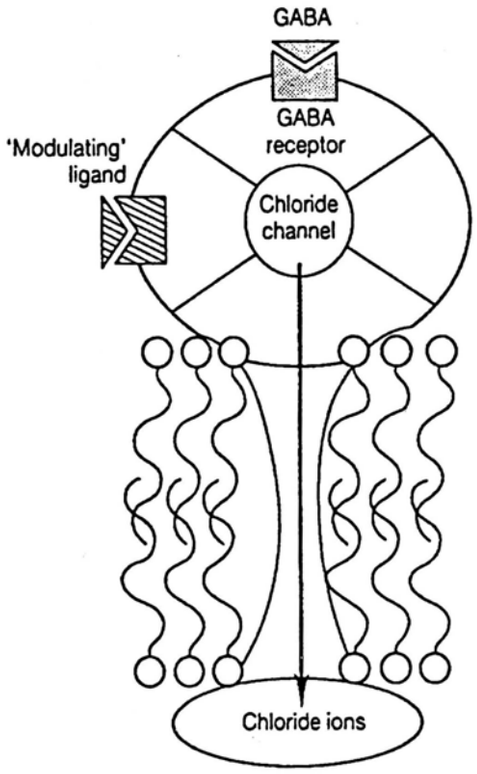


FIGURE 1. 2. Schematic model of $GABA_A$ - receptor chloride inophore and proposed molecular mechanism of propofol. Reproduced with permission from Salonen MA and Maze M. Molecular mechanism of action for hypnotic and sedative agents in *Mechanisms of Drugs in Anaesthesia*, eds Feldman S, Scurr CF, Paton W. Copyright 1993, the Edward Arnold Limited.

Central nervous system effects

The onset of anaesthesia following intravenous propofol occurs within one arm-brain circulation time. It has been explained by the short blood

brain equilibration half-life of 2.9 minutes in adult study [Schüttler, Schwilden, and Stoeckel, 1986]. The incidence of pain on injection is about 30% when injected into small veins of the hand and lower when the antecubital fossa vein is used [Lees, McCulloch, and Mair, 1985; Stark *et al*, 1985]. The incidence of pain on injection was found to be 5.2% in the recent analysis from the phase IV study [McLeskey *et al*, 1993]. Other effects include excitatory effects, such as spontaneous movements [Fahy, van Mourik, and Utting, 1985], hypertonous, or hiccup [Steegers and Foster, 1988]. Seizures after propofol have been estimated as occurring one in 47,000 administrations by the Committee on the Safety of Medicines in the United Kingdom [Bevan, 1993]. The central nervous system depression is dose-related. It has a short duration of action. The fast redistribution and metabolism contribute to the rapid decline in plasma concentrations and awakening from anaesthesia [Kanto and Gepts, 1989]. Compared with other anaesthetic agent, recovery after propofol is pleasant and patients report being particularly " clear headed" [Steegers and Foster, 1988].

Dose requirements

The effective bolus dose of propofol for induction of anaesthesia in 95% of healthy unpremedicated adult patients has been found to be 2.5 $mg.kg^{-1}$ in a multicentre trial [Cummings *et al*, 1984]. Premedication with opioids or benzodiazepines decreased the induction dose of propofol, but had very little effects on the induction characteristics [Briggs *et al*, 1985]. Propofol used for total intravenous anaesthesia has been studied in various anaesthetic protocols; as a bolus followed by incremental doses, zero-order infusion, manually controlled infusion and computer controlled infusion with or without opioids or nitrous oxide supplements. The dose requirements reported have varied widely depending on premedication and supplementary agents used during anaesthesia.

Cardiovascular effects

Induction of anaesthesia with propofol causes a significant reduction in systemic arterial pressure (15-30%) because of decrease in cardiac output [Monk *et al*, 1987; Lippmann *et al*, 1988], decrease in systemic vascular resistance (SVR) [Claeys, Gepts, and Camu, 1988] or both [Grounds *et al*, 1985; Coates *et al*, 1987; Gauss *et al*, 1991]. It also resets the baroreflex to allow slower heart rates [Cullen *et al*, 1987]. A recent study by Fairfield and colleagues [1991] has suggested that the conflict in the cardiovascular data was due to the biphasic effect of propofol on the cardiovascular system. An immediate marked reduction in SVR with an associated tachycardia, an increase in cardiac output, and a decrease in arterial pressure was followed by a phase of increased in SVR towards the baseline value, a decrease in heart rate and cardiac output, and a further decrease in arterial pressure. In an animal study, it was suggested that the cardiovascular depression observed *in vivo* was not related to intrinsic myocardial depression [Riou *et al*, 1992]. When compared with other i.v. anaesthetic agents, propofol causes a greater reduction in arterial pressure than thiopentone [Grounds *et al*, 1985; Fahy, van Mourik, and Utting, 1985; Lippmann *et al*, 1988] and methohexitone [MacKenzie and Grant, 1985a; Gold, Abraham, and Herrington, 1987; Doze, Westphal and White, 1987; O'Toole *et al*, 1987]. The haemodynamic response may be advantageous in attenuating the hypertensive response during laryngoscopy which has been confirmed by various studies [Monk *et al*, 1987; Coates *et al*, 1987; Coley *et al*, 1989; Fahmy *et al*, 1990; Gin *et al*, 1993].

Respiratory effects

Propofol causes respiratory depression. After induction with propofol, variable incidence of apnoea (up to 80%) have been reported [Taylor *et al,* 1986; Gold, Abraham and Herrington, 1987; Goodman, Black, and Carter, 1987]. Noninvasive respiratory measurements have demonstrated that propofol causes a significant reduction in tidal volume, minute volume, mean inspiratory flow and functional residual capacity [Taylor *et al,* 1986; Goodman, Black and Carter, 1987; Grounds *et al,* 1987]. The ventilatory depression after propofol is greater than after thiopentone [Taylor *et al,* 1986]. The effect was enhanced by the opioid premedication. Goodman and colleagues [1987] also found that propofol blunts the ventilatory response to an increase in inspired carbon dioxide. A greater degree of relaxation of the upper airway was observed after propofol compared with thiopentone [McKeating, Bali, and Dundee, 1988]

Other effects

Propofol has no adverse effects on liver [Kawar *et al,* 1982; Stark *et al,* 1985] and renal function [Stark *et al,* 1985]. Life threatening anaphylactoid reactions following propofol administration have been reported to be hypersensitivity reaction to propofol [Laxenaire *et al,* 1988; Laxenaire *et al,* 1992; McHale and Konieczko 1992]. The incidence of seizures after propofol has been estimated to be 1 in 47,0000 administrations according to the Safety of Medicines in the United Kingdom [Committee of Safety of Medicines, 1987; Bevan, 1993]. A consistent feature observed with propofol is the low incidence of postoperative nausea and vomiting [Stark *et al,* 1985; McCollum, Milligan, and Dundee, 1988].

Propofol in Paediatric Anaesthesia

Propofol, after establishing a significant place in adult anaesthesia, was first used in children in 1985 [Purcell-Jones and James, 1985]. Since then clinical trials have been carried out in Europe and, later, in North America [Purcell-Jones *et al*, 1987; Morton *et al*, 1988; Mirakhur, 1988; Puttick and Rosen, 1988; Valtonen *et al*, 1988; Patel *et al*, 1988; Valtonen *et al*, 1989a; Hannallah *et al*, 1991].

Pharmacokinetic profile

Propofol pharmacokinetic variables in children have been estimated by studying the blood concentration-time profiles after a single dose [Saint Maurice *et al*, 1989; Valtonen *et al*, 1989a; Jones, Chan and Andrew, 1990] and during continuous infusion [Marsh *et al*, 1991, Kataria *et al*, 1994]. The paediatric blood-concentration time-profile after a single dose is best described by a three-compartment model as in adults. There are some variations in the results, probably from the differences in the methodologies. Jones and colleagues [1990] suggested that the influence of ethnic origin on metabolism may have contributed to a shorter elimination half-life observed in their study. However, there is a general agreement among the studies, that the metabolism and clearance of propofol in children is higher than that in adults. These results imply that children are likely to require a larger dose for induction of anaesthesia and a higher infusion rate to maintain a similar blood concentration as adults. This has been confirmed by induction dose response studies of propofol [Patel *et al*, 1988; Hannallah *et al*, 1991; Westrin, 1991] and infusion studies in children between three and 12 years old [Marsh *et al*, 1991; Browne, Prys-Roberts, and Wolf, 1992].

Pharmacodynamic profile

Central nervous system effects

A dose of 2.5 - 3.0 $mg.kg^{-1}$ is required in unpremedicated children to ensure a smooth transition to an inhalational-maintenance technique [Hannallah *et al*, 1991]. Premedication reduces the requirement to 2.0 $mg.kg^{-1}$ [Patel *et al*, 1988]. The onset of anaesthesia is fast, The mean onset time of 31 (SD 8.31) s was comparable with that of thiopentone (29 (SD 3.44) s) [Purcell-Jones *et al*, 1987].

Spontaneous involuntary movements after propofol appear to occur more frequently in children with the incidence reported ranging from 10 - 75% [Borgeat *et al*, 1991, Morton *et al*, 1992]. The movements have been shown to be dystonic and choreiform in nature. However, detailed study with EEG tracings during induction showed no EEG abnormalities suggesting them to be subcortical in origin [Borgeat *et al*, 1991]. Neurological side effects including seizures following propofol (during early recovery period and late onset) have been reported in adults and children [Laycock GJA 1988; Wittenstein and Lyle, 1989; Paech and Storey, 1990; Saunders and Harris, 1990; Thomas and Boheimer, 1991; Trotter and Serpell, 1992; Bevan, 1993; Finley *et al*, 1993]. Most of these episodes were transient and resolved spontaneously, although occasionally some persisted for a longer time. Athetoid movements and opisthotonus are the unusual features that are seen after anaesthesia which are almost confined to propofol [Bevan, 1993]. The cause for these excitatory adverse effects is unclear. The association between propofol and epileptogenic activity is controversial, because it is known to reduce the length of seizures during electroconvulsive therapy [Dwyer et al, 1988], and has been used successfully in controlling status epilepticus [Wood, Browne, and Pugh, 1988; Yanny and Christmas, 1988]. There were

suggestions that fentanyl and alfentanil may potentiate the effect of propofol [Laycock, 1988; Wittenstein and Lyle, 1989].

The incidence of pain on injection in adults is higher when small veins on the dorsum of the hand are used rather than in the antecubital fossa [McCulloch and Lees, 1985; Stark *et al*, 1985; Scott, Saunders, and Norman, 1988]. It is therefore, expected that the incidence in children would be higher than in adults. The incidence in various paediatric studies ranges from 24 - 85% [Morton *et al*, 1992]. Lignocaine 1 mg mixed with propofol 3 mg has been shown to abolish the pain on injection in the veins of the dorsum of the hand in a study of 50 unpremedicated children [Morton, 1990]. The minimum effective dose of lignocaine required to prevent pain on injection has been reported to be 0.2 $mg.kg^{-1}$ by the same group [Cameron *et al*, 1992]. Venous sequelae are rare [Hannallah *et al*, 1991; Morton *et al*, 1992].

Recovery in children after propofol induction has found to be faster than after thiopentone [Mirakhur, 1988, Valtonen *et al*, 1988; Valtonen *et al*, 1989a; Runcie *et al*, 1993]. Similar findings have been found with anaesthesia using propofol for both induction and maintenance [Puttick and Rosen, 1988, Borgeat *et al*, 1990; Larsson, Asgeirsson, and Magnusson, 1992], whereas no difference in the recovery time after total propofol anaesthesia has been found in comparison with halothane anaesthesia [Martin, Nicolson, and Basgas, 1993], propofol followed by halothane [Doyle, McFadzean, and Morton, 1993]. The other advantage is a lower incidence of nausea and vomiting after propofol than after thiopentone, halothane or isoflurane anaesthesia [Watcha *et al*, 1991; Larsson, Asgeirsson, and Magnusson, 1992; Martin, Nicolson, and Basgas, 1993; Snellen, Vanacker, and van Aken, 1993; Weir *et al*, 1993;].

Cardiovascular effects

Induction of anaesthesia in children is associated with a 15-25% reduction in systemic arterial pressure as in adults [Mirakhur, 1988; Morton *et al*, 1988; Purcell-Jones *et al*, 1987; Valtonen *et al*, 1988; Saarnivaara, Hiller and Oikkonen, 1993]. This is associated with an initial increase in heart rate which then settles to the baseline or less with halothane maintenance. It has been suggested that the initial rise in heart rate was due to pain on injection [Morton *et al*, 1992]. A recent study on QT interval and heart rate during induction in children found that propofol causes prolongation of the QT interval and results in a higher incidence of bradycardia and junctional rhythm than with thiopentone or methohexitone [Saarnivaara, Hiller, and Oikkonen, 1993]. There was no data on the mechanism of the hypotension in children.

Respiratory effects

The incidence of apnoea during induction of anaesthesia with propofol in children ranges from 11 to 48% and is the same as that following thiopentone, but more frequent than after inhalational induction with halothane [Morton *et al*, 1992]. Apnoea is usually transient but can last for over one minute. Premedication appears to increase the duration and incidence of apnoea. Other adverse respiratory effects such as hiccough, coughing, and laryngospasm are similar to those after thiopentone induction.

Clinical experience

There is an increasing experience in using propofol as a single-bolus induction followed by either inhalational agents or propofol infusion for maintenance of anaesthesia in children over three years of age for various general surgical, ENT, ophthalmic and dental procedures. In a recent study of cardiac surgery for children, propofol, in doses sufficient to produce burst

suppression on the EEG during cardiopulmonary bypass was found to reduce whole body oxygen requirements and the glucose and cortisol responses without increasing blood lactate concentrations. There was no increase in inotropic requirements and recovery was satisfactory [Laycock *et al*, 1991a; 1991b; 1992]. Propofol has been found to be superior to thiopentone in sedation for diagnostic procedures such as CT scanning [Valtonen *et al*, 1989b], magnetic resonance imaging [Vangerven *et al*, 1992; Bloomfield *et al*, 1993], and radiation therapy [Deer and Rich, 1992]. Airway control was satisfactory and recovery was faster than with thiopentone [Valtonen *et al*, 1989a]. The safety of propofol for sedation in intensive care unit is not yet established. A recent report on five children with respiratory tract infection in whom metabolic acidosis, lipaemia, and death from fatal myocardial failure, after the use of propofol, has caused much concern [Parke *et al*, 1992]. The exact mechanism of these fatal incidents remains uncertain.

Children are ideal patients for day surgery [Morris, 1992]. A large proportion of paediatric surgery is for minor procedures that can be performed as day cases. This reduces the period of separation from parents and a familiar environment. Furthermore they are invariably accompanied by adults who provide supervision and care during the postoperative period. In North America, up to 60% of paediatric surgical patients are managed on a day-care basis [Steward, 1986]. In the United Kingdom, there is an increase paediatric day care surgery. Propofol, with its rapid elimination, has been shown to be a suitable anaesthetic agent for day-case anaesthesia in adults and it should be a potential alternative to thiopentone in children. Propofol has been shown to have a great potential as an agent for induction and maintenance of sedation and anaesthesia in children in the western hemisphere and a thorough evaluation of this agent in the Asian paediatric population is now warranted.

RESEARCH PLAN

Paediatric research into propofol has been mostly on children over three years old. The studies in this thesis have been designed to investigate children from six months to twelve years of age. Short surgical cases without premedication were used in most of the studies to simulate a day-case setting.

As growth in children is a dynamic process, the dose of propofol required in children of different ages may vary. The dose required for induction was determined in three groups of children: those aged less than two years, those between two and five years, and those between six years and 12 years old, using ED_{50} and ED_{95} for loss of the eyelash reflex and the acceptance of a face mask for the estimation. These end points were similar to those used in other paediatric studies to enable comparisons to be made. The induction characteristics of propofol were studied in comparison with thiopentone. Propofol causes a significant decrease in arterial pressure during induction of anaesthesia both in adults and children. Two studies were performed on the haemodynamic responses of propofol. Haemodynamic changes in response to different doses were studied during the dose finding investigation. Although the mechanism has been extensively studied in adults, it has not been investigated in children. The mechanism of cardiovascular response following propofol induction was conducted using a non-invasive technique of pulse-Doppler and two-dimensional echocardiography to measure the cardiac output and the derived cardiovascular parameters. The incidence of apnoea and pain on injection were also determined during the induction studies.

The single bolus pharmacokinetic variables for propofol were determined in children between one and 12 years of age, by studying the blood concentration-time profiles after 2.5 $mg.kg^{-1}$ of intravenous propofol.

This was to examine for any age-related difference in kinetics that might account for the difference in dose requirements in the children of different age groups. Plasma protein binding of propofol was compared with that of adults.

The development of computer-controllable infusion pumps has made administration of total intravenous anaesthesia easier and more precise than using manual-infusion pumps. Propofol infusion for induction and maintenance of anaesthesia was evaluated in children using a computer infusion pump. This enabled the paediatric pharmacokinetic algorithm which was recommended in the literature to be evaluated in the local paediatric population. The anaesthesia and recovery characteristics of the propofol infusion technique was then compared with three relatively more conventional techniques using either thiopentone, propofol or halothane for induction followed by halothane for maintenance.

SECTION II
METHODS

CHAPTER 2

Methods

RESEARCH METHODS

Ethical consent

All studies were approved by the Clinical Research Ethics Committee of the Faculty of Medicine of the Chinese University of Hong Kong. Informed consent from both parents of all the patients were obtained before the study.

Patient selection and Anaesthesia

Only healthy children were studied. Those with a history of allergy or adverse reactions to previous anaesthesia and those who were distressed or not amenable to coaxing were excluded from the study. Children with a haemoglobin level less than 11.5 $g.dl^{-1}$ were excluded from research involving blood sampling *i.e.* pharmacokinetic studies.

Children were not premedicated except for those in the cardiovascular part of the study, who received oral diazepam 0.4 $mg.kg^{-1}$ about one to two hours before anaesthesia to ensure that they were not distressed during the measurement of cardiovascular parameters before the induction of anaesthesia. All children had EMLA emulsion cream (lignocaine 25 $mg.g^{-1}$ and prilocaine 25 $mg.g^{-1}$), [Astra Pharmaceuticals, Sweden] applied to the dorsum of both hands about an hour before anaesthesia and were then covered with an impervious dressing.

One of the veins under the EMLA cream patch was selected for intravenous cannulation for both drug and fluid administration. Another intravenous cannula was inserted in the contralateral arm after the patient was asleep for obtaining blood samples if required. All patients were monitored in accordance with the minimum standards set by the Association of Anaesthetists of Great Britain and Ireland and the Australian and New Zealand College of Anaesthetists. The monitoring included pulse

oximetry (Datex Satlite, Datex Instrumentarium Corp, Helsinki, Finland), end-tidal capnography (HP 78356A, Hewlett-Packard, California, USA.), and pulse rate and noninvasive automatic arterial pressure monitor (Dinamap 1846SX, Critikon Inc., Florida USA). Anaesthesia was induced by either propofol or thiopentone according to the protocol. Standard techniques were used for maintenance of anaesthesia. Specific methods of anaesthesia used are outlined in the method section of the individual studies when relevant.

All comparative studies were randomised using the sealed envelope technique. A separate stack of sealed opaque envelopes was prepared for each stratum within which randomisation took place. Stratification were set in studies involving large sample of patients covering wide age range, as this was believed to be a confounder of the effects studied. The observers were blind to the anaesthetic agent given. For the noninvasive measurement of cardiac output by two-dimensional echocardiography, a single paediatric cardiologist was invited to perform the measurements. For the recovery study, a single research nurse was recruited to do the psychomotor testing.

EQUIPMENT

Echocardiography

Cardiac output was measured noninvasively by the technique of pulsed Doppler echocardiography. Cardiac output measurements by this method has been shown to be reliable and highly reproducible [Alverson *et al* , 1982; Rein *et al,* 1986; Mellander *et al* , 1987]. Doppler derived cardiac output has good correlation with that by dye dilution technique (r = 0.93 - 0.98). The 95% confidence limits for the difference between the two techniques was -16% to +12% of the mean cardiac output [Tibballs, Osborne, and Hockmann, 1988a]. However, Doppler technique has several limitations. The accuracy in cardiac output determination is dependent on the measurements of aortic diameter and mean blood flow velocity. Most investigators used the aortic diameter to derive the cross - sectional area ($CSA = \pi \times r^2$). Accurate imaging of the area may be difficult at times. Cardiologists compensate this by ensuring that the ultrasound beam is in parallel alignment to the velocity vector (incidence angle less than 20°) to obtain the most accurate blood flow velocity. The accuracy may also be affected by motion. Patients with neck deformity, abnormal aortic valve or arch, or surgical emphysema are difficult to study. Doppler echocardiography, because of its noninvasive nature and its ability to provide information on a beat-to beat basis, is useful in assessing the changes in stroke volume and cardiac output more accurately than in determining the absolute flow rate, owing to cancellation of systemic errors [Calafiore, and Stewart, 1990]

Stroke volume was measured by an ultrasound scanning device (Aloka-280, Aloka Co.,Ltd., Tokyo, Japan) using a handheld Doppler probe of 5 MHz. An initial two-dimensional echocardiogram was scanned along the parasternal longitudinal axis to obtain the internal aortic diameter at the

aortic annulus. Three measurements were performed and the average was taken as the aortic diameter. Pulsed-wave Doppler signals from the ascending aorta were then identified and recorded by placing the transducer probe at the suprasternal notch. The transducer was positioned to align the transmitted sound beam as parallel as possible to the velocity vector of the blood flow. All the computations were performed by the built-in program of the ultrasound scanner. The Doppler recordings and ECG tracings were recorded on videotape for later analysis.

A two-dimensional echocardiography was chosen because it is more accurate than M- mode echocardiography. M-mode calculates volume from a measurement in a single dimension, and therefore any error made during the measurement could be magnified in the subsequent calculations [Slavik, 1988]. The diameter of the aortic annulus was measured because it does not change during systole and therefore calculation of cardiac output using measurement at this site agrees more closely with invasive techniques than using aortic root measurements [Rein *et al,* 1986]. Pulsed Doppler has been suggested to be a better technique than continuous Doppler. Pulsed Doppler permits measurement of flow velocity by range-gating at the specified location (eg: the aortic orifice), whereas continuous wave Doppler measures velocity along the entire beam path and may include an area with a parabolic velocity profile which may give a misleading mean spatial velocity [Tibballs, Osborne and Hockmann, 1988a].

The velocity of the blood flow was calculated by the Doppler equation:-

$$V = \Delta f c / 2 fo$$

Any deviation of the transducer from the parallel axis of more than 20° angle was corrected by the formula:-

$$V = \Delta f c / 2 fo \ Cos \theta$$

where V = velocity of blood flow; Δ f = change in frequency; c = sound velocity in the blood; fo = transmitting frequency; θ = angle of insonance or the angle between the beam of ultrasound and the direction of blood flow.

Stroke volume (SV) was computed by multiplying the average time velocity integral by the aortic cross-sectional area using the formula:-

$$SV = CSA \sum_{t=0}^{t=ET} V \Delta t$$

where CSA = cross sectional area of aorta, V= velocity, t = sampling interval and ET = ejection time.

The stroke volume was calculated by averaging the measurements obtained from three consecutive cardiac cycles.

Cardiac output was calculated by the product of stroke volume and heart rate. Surface area was derived from a nomogram for infants and children [*Documenta Geigy*, 1970] to calculate the stroke volume index and cardiac index. Systemic vascular resistance (SVR) was calculated using the following formula [Kaplan, 1987].

$$\text{SVR (dynes. sec. cm}^{-5}) = \frac{\text{Mean arterial blood pressure}}{\text{Cardiac output}} \times 80$$

Arterial pressure monitor

Arterial pressure was recorded using an automatic blood pressure recorder (Dinamap 1846SX, Critikon Inc., Florida, USA). Dinamap apparatus has been assessed in children of various age groups [Friesen and Lichtor, 1981; Park and Menard, 1987]. Using Dinamap, systolic pressure was 0.94 (intraarterial reading) + 3.54 (r= 0.96) and diastolic pressure was 0.98 (intraarterial reading) + 1.7 (r= 0.94) in neonates [Friesen and Lichtor, 1981]. In infants and children, 90% of patients had an error of 5 mm Hg or less for systolic pressure, and 72% of patients had an error of 5 mm Hg or less for diastolic and mean pressures. Correlation coefficients for systolic was 0.970; diastolic 0.903 and mean arterial pressure 0.917 [Park and Menard, 1987]. These studies conclude that oscillometric determination of arterial pressure with the Dinamap is reliable and accurate in infants and children. However, its functions may be affected by poor peripheral pulsation, severe dysrhythmia and motion artifacts.

Pulse oximeter

Arterial oxygen saturation was monitored by Datex Satlite (Datex Instrumentarium Corp. Helsinski, Finland). This apparatus was assessed by Clayton and colleagues [1991]. They have shown that 95% of readings were within 3% of the reference value (co-oximeter reading which was taken as standard). The assessment has ranked this apparatus to be high on the list of performance in terms of a combination of accuracy, precision, and the number of readings within 3% of the reference reading. Although pulse oximeter is a standard component of anaesthetic monitoring, errors in SaO_2 reading can occur from various influences such as motion, ambient light, presence of abnormal haemoglobin. SaO_2 is also underestimated in low SaO_2 (<70%).

ASSAY OF PROPOFOL

The assay of propofol concentration in whole blood was measured by high performance liquid chromatography (HPLC) [Plummer, 1987; Chan and Gin, 1990]

Propofol is significantly bound to the formed elements of blood and therefore, whole blood is the preferred sample for analysis [Plummer, 1987]. Blood samples were collected in lithium-heparin tubes and stored at 4°C until analysis. Stability tests showed that propofol in blood samples was stable for a period of three months. The average recovery of propofol from whole blood was 93% (range 90-98%) at 500 $ng.ml^{-1}$.

All chemicals used were of analytical grade unless specified otherwise. Cyclohexane, 0.1M sodium dihydrogen phosphate, glacial acetic acid and thymol were supplied by British Drug House, Poole, United Kingdom, tetramethylammonium hydroxide by Sigma Chemical Company, St Louis, USA, and acetonitrile HPLC grade by Mallinckrodt Inc, Paris, Kentucky, USA. The mobile phase consisted of 66% (v/v) acetonitrile in distilled water containing 1% (v/v) glacial acetic acid. The operating pressure was 5330 kPa and the solvent flow rate was 1.6 $ml.min^{-1}$. Glacial acetic acid was used in preference to trifluoroacetic acid to prevent the possible corrosion of the pump by the latter.

The HPLC consisted of the following components: the solvent delivery system (M510 pump, Waters, Milford, USA), injector (Rheodyne 7125, Cotati, California, USA), C_{18} reversed phase column (Nova Pak in a Waters RCM compression module, Waters, Milford, USA) linked to a C_{18} pre-column, fluorometric detector (HP 1046A Hewlett Packard Waldbronn, Germany) with excitation and emission wavelengths set at 276 nm and 310 nm respectively and integrator (HP 3396 A, Hewlett Packard, Avondale Pennsylvania, USA).

The internal standard thymol (12 ng in 50 µl), 0.1M sodium dihydrogen phosphate buffer pH 4.6 (1 ml) and 5 ml cyclohexane were added to the blood sample (0.5ml). After mixing for 15 minutes, the samples were centrifuged at 20°C for 15 minutes at 3000 rpm. The organic extract (cyclohexane layer) was transferred into a tapered glass tube and made alkaline by adding tetramethylammonium hydroxide (50 µl) and evaporated to dryness at 37°C under a gentle stream of nitrogen. The residue was redissolved in acetonitrile (80 µl). The concentrate (10-15 µl depending on the concentration) was analysed by HPLC with fluorometric detection. An additional standard (whole blood with known concentration of propofol) was used at the beginning and end of each run (approximately 14 samples). Each sample run took seven min with the internal standard appearing at 3.5 min and propofol at 5.2 min.

Calibration graphs were used for each batch and constructed from the mean of three trials at six concentrations of propofol . A known amount of "pure" propofol was weighed and serial dilutions were made to prepare stock solutions containing 100 $\mu g.ml^{-1}$, 10 $\mu g.ml^{-1}$, 1 $\mu g.ml^{-1}$ of propofol. Aliquots of these stock solutions were then added to propofol free blood to prepare the calibration standards which ranged from 50 to 3000 $\mu g.ml^{-1}$ (Figure 2.1). The calibration graphs relating the peak height ratios and concentration of propofol were linear over the range of 2 to 3000 $ng.ml^{-1}$ with intra-assay coefficient variation ranging from 9.96% at 50 $ng.ml^{-1}$ to 1.81% at 3000 ng. ml^{-1} (mean 4.17%). The inter-assay coefficient of variation were 6.4% at 50 ng.ml $^{-1}$ and 5.4% at 3000 ng.ml $^{-1}$. The lower limit of quantification was approximately 2 $ng.ml^{-1}$. The calibration data are listed in the appendix B (page 190).

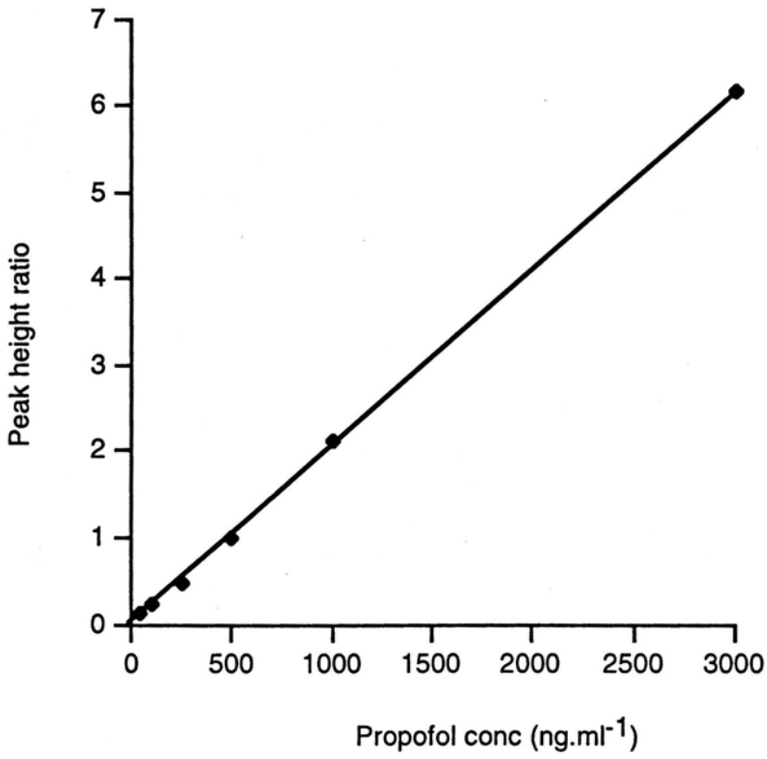


FIGURE 2. 1. Calibration graph for propofol, r = 0.999

PROTEIN BINDING METHODS

Protein binding studies were carried out by equilibrium dialysis using an equilibrium dialyser (Spectrum, Texas, USA).

Component of the system consisted of an equilibrium dialyzer with a Spectrapor 2 dialysis membranes with a molecular weight cut off of 12,000 to 14,000. The dialysis buffer was Sørensen's phosphate buffer made isotonic with sodium chloride (pH 7.4).

Blood samples were collected in lithium-heparin tubes. The blood samples were immediately centrifuged at 3000 rpm, 20°C for 10 minutes. The plasma was separated and stored at -70°C before analysis. A known concentration of propofol (usually 3000 $ng.ml^{-1}$) was added to plasma and incubated for one hour at 37°C. Plasma samples (1 ml) containing propofol were dialysed against phosphate buffer (1 ml) without propofol in the dialyzer for 4 hours in a water bath at 37°C with a rotation speed of 15 rpm. After dialysis, samples from both the plasma and buffer chamber were then analysed for propofol content by HPLC. The percentage of protein binding was then calculated by the following formula.

$$\% \text{ bound drug} = (C_p - C_{bu})/Cp \times 100$$

where C_p = drug concentration in plasma and C_{bu} = drug concentration in buffer.

Recovery of propofol was 100.6% when 500 $ng.ml^{-1}$ was added (CV 3.97%) and 104.3% (CV 5.03%) when 3000 $ng.ml^{-1}$ was added. The inter-assay coefficients of variation were 0.45% at 500 $ng.ml^{-1}$ and 0.39% at 3000 $ng.ml^{-1}$. The intra-assay coefficients of variation were 0.46% at 500 $ng.ml^{-1}$ and 0.5% at 3000 $ng.ml^{-1}$.

PHARMACOKINETIC ANALYSIS

Bolus dose study

The blood concentration-time profiles after single intravenous bolus administration were analysed by a model-independent method based on statistical-moment theory and a compartmental method using the pharmacokinetic software packages MKMODEL (version 4.0, BIOSOFT, Cambridge, UK) [Cockshott and Haywood, 1992] and PKCALC [Shumaker, 1986] running on an IBM compatible XT computer. The curve-stripping technique in the PKCALC program was used to estimate the number of points in the terminal log-linear portion of the concentration-time plots for the model independent method and to provide the initial estimates (Vc, Cl, k_{21}, α, β, γ) for the compartmental analysis.

The MKMODEL program was used to perform the following analysis.

Moment Analysis.

The area under the concentration-time curve (AUC) from zero and infinity and area under the concentration-time moment curve (AUMC) from zero time to infinity were calculated by the log-trapeziodal rule. For the purpose of this calculation, the concentration at time zero was taken as equal to the concentration at two minutes.

Estimation of the infinite part of the curve was obtained using the formula: $t'C_p/L_z$

where $t'C_p$ is the drug concentration measured of the last blood sample and L_z is the overall elimination constant.

Estimation of the infinite part of the AUMC was obtained using the formula: $t'C_p/L_z \times (t' + 1/L_z)$

where t' is the time that the last blood sample was collected.

Clearance {Cl(NC)}, mean residence time {MRT}, apparent volume of distribution at steady state {V_{ss}} were calculated from the following formulae:

$$Cl(NC) = Dose/AUC$$

$$MRT = AUMC/AUC$$

$$V_{ss}(NC) = Cl(NC) \times MRT$$

Compartmental analysis.

Individual concentration-time data sets were fitted to the following tri-exponential equation:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

where C_t = concentration at time t; A, B and C are intercepts and α, β, and γ are the slopes of the three exponential lines.

$$A = \frac{X_0 (k_{21} - \alpha) (k_{31} - \alpha)}{V_c (\alpha - \beta) (\alpha - \gamma)}$$

$$B = \frac{X_0 (k_{21} - \beta) (k_{31} - \beta)}{V_c (\beta - \alpha) (\beta - \gamma)}$$

$$C = \frac{X_0 (k_{21} - \gamma) (k_{31} - \gamma)}{V_c (\gamma - \beta) (\gamma - \alpha)}$$

where X_0 = bolus dose of propofol
V_c = central volume of distribution
α, β and γ are the hybrid rate constants

k_{21}= the micro rate constant describing transfer from the shallow peripheral compartment to the central compartment

k_{31} = the micro rate constant describing transfer from the deep peripheral compartment to the central compartment calculated using the formula:

$$\frac{\alpha \cdot \beta \cdot \gamma \cdot V_c}{k_{21} \cdot \text{clearance}}$$

The volume of central compartment (Vc), clearance (Cl) and the hybrid constants giving the best fit were derived using the non-linear regression program in MKMODEL. The distribution and elimination half-lives ($t_{1/2\alpha}$, $t_{1/2\beta}$, $t_{1/2\gamma}$), the micro rate constants were calculated using the standard formulae [Gibaldi and Perrier, 1982].

Infusion and pharmacokinetic modelling

For the infusion study, an algorithm for pharmacokinetic model controlled infusion for paediatric patients which had already been prospectively tested [Marsh *et al* , 1991] was used to evaluate its suitability and accuracy in the local paediatric population. After a pilot study of ten patients, the pharmacokinetic algorithm was modified using an iterative linear least-squares regression program. Propofol dosage required to maintain the desired blood concentration was delivered using an IBM compatible 386SX laptop computer connected via a RS232C serial interface to a computer controllable infusion pump (Ohmeda 9000, Medishield, UK) to control the infusion rate. A program was written in 'C' (Turbo C, Borland, USA) to control the pump and provide graphs of blood concentration and infusion rates.

The dose to maintain a constant blood level of propofol was based on patient weight. An initial bolus of propofol was delivered by zero order infusion at the infusion pump's top rate (1200ml. hr^{-1}) to achieve the desired concentration rapidly according to the formula:

$$A_1 = C. V_1. W \qquad \text{(Equation 1)}$$

where A_1 is the amount of drug in the central compartment, C is the desired concentration in the central compartment in $ng.ml^{-1}$, V_1 is the volume of central compartment in $l.kg^{-1}$ and W is the patients body weight in kilograms. A modification of Euler's numerical integration technique [Shafer *et al*, 1988, Maitre and Shafer, 1990] was used to calculate drug concentrations in the central compartment, so that infusion rate was constantly altered to maintain a constant theoretical blood level. Thus for a three compartment open model:

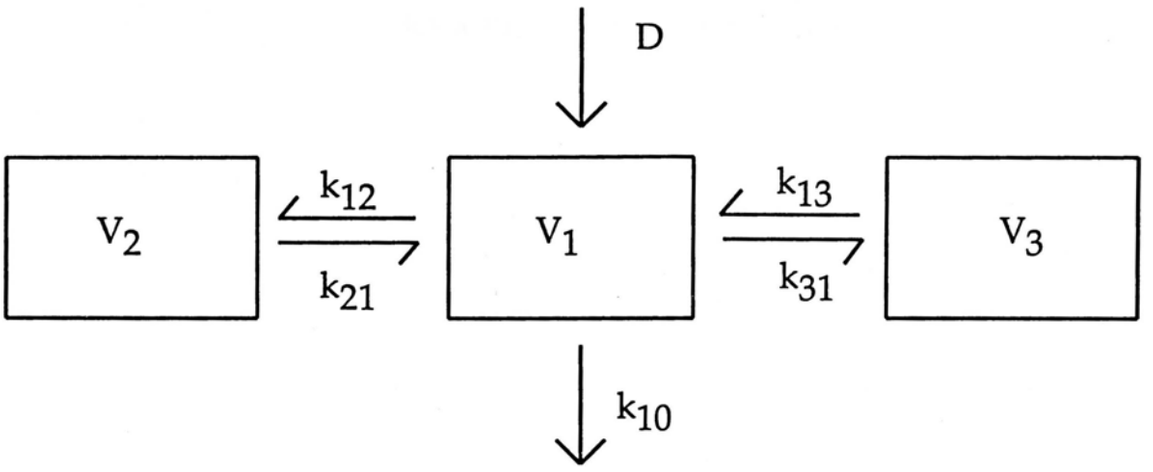
$$A_1' = A_1 + [k_{21} A_2 + k_{31} A_3 - (k_{10} + k_{12} + k_{13}) A_1 + R].\Delta t$$

where $A_2' = A_2 + (k_{12} A_1 - k_{21} A_2).\Delta t$

$$A_3' = A_3 + (k_{13} A_1 - k_{31} A_3).\Delta t$$

and therefore $R = (A_1' - A_1).\Delta t^{-1} - k_{21}A_2 - k_{31}A_3 + (k_{10} + k_{12} + k_{13}) A_1$

where A_1, A_2, A_3 are the amount of drug in compartments 1,2 and 3; k_{12}, k_{21}, k_{13}, k_{31}, k_{10} are the rate constants for transfer into and out of the peripheral compartments and elimination respectively (Figure 2.2); t = time and R = the infusion rate. A_1' is the next value of A_1. The initial value of A_1 was taken from equation 1, with no allowance made for time taken for infusion of the bolus. The algorithm was iterated every ten seconds. The desired concentrations were adjusted according to standard clinical criteria, increases in concentration being made using bolus doses to make up the difference between current and desired amount of drug in the central compartment using equation 1 and decreases being made by switching off the pump and allowing the plasma concentration to decay until the new target concentration was reached. The algorithm for altering plasma concentrations was based on one described by White and Kenny [1990]. The model assumes that the drug effect is proportional to the concentration in the central compartment, that drug elimination is from the central compartment and that clearance is constant over the concentration range used.



D = initial dose

V_1 = 0.432 ml kg^{-1}

k_{10} = 0.0967 min^{-1}

k_{12} = 0.1413 min^{-1}

k_{13} = 0.0392 min^{-1}

k_{21} = 0.1092 min^{-1}

k_{31} = 0.0049 min^{-1}

FIGURE 2.2. Three-compartment open model for infusion of propofol

STATISTICAL METHODS

The individual statistical methods used in this thesis are described in the "methods" section in each chapter. Parametric and nonparametric methods were used where appropriate. Included in the list of parametric methods were the paired t-test, two sample t-test, Pearson correlation, analysis of variance (ANOVA), repeated measures ANOVA and probit modelling. Nonparametric methods used were Wilcoxon-Mann-Whitney test, Kruskal-Wallis test, the Spearman correlation test, the Chi-square test and Fisher's exact test for contingency tables. Data in the text are presented with mean (SD or CI) or median (range) as relevant. All test assumptions were examined before a test is used. For example, normality of the data was assessed using half-normal plots and the Shapiro-Wilk statistic [Shapiro and Wilk, 1965]. If the data was found to have violated the test assumptions, suitable transformations of the data were made or alternative test procedures employed. In all statistical analysis, a type I error of 0.05 and a type II error of 0.2 was allowed, except where otherwise stated. To control the two types of errors to these levels, sample sizes were calculated based on the appropriate formulae. These sample sizes were then used as reference to gauge the size of the study.

Probit analysis [Finney, 1971] was used in the quantal dose study. In this method, binary response variables based on cohorts of patients under different doses were measured and a dose response relationship was estimated on the log-dose scale. The relationship was linearized by a probit, logit or gompit transformation. Goodness of fit of the data to a particular transformation was performed by a Pearson's goodness-of-fit test. Differences between different age groups were inferred by testing the nullity of a group parameter. Parallelism of probit lines was tested using the parallelism chi-square. ED_{50} and ED_{95} were obtained using Fieller's Rule.

When parallelism between probit lines holds, relative potencies of the different groups can be obtained by taking the respective ratios of the ED_{50}.

Repeated Measures ANOVA was used when appropriate to analyse responses that were measured repeatedly over time. This was performed by PROC GLM of the SAS package (SAS Institute Inc, Cary, NC, USA). In this method, analyses were performed on differences in the responses over time between groups, and time-group interaction, where significant interaction suggested that the differences were not constant over time. In the presence of non-constant group differences over time, differences between groups were further examined at different time points. A multivariate or pooled univariate test was used to test differences between groups. The data were subjected to a sphericity test for choosing the appropriate test. If $p > 0.2$ from this test, the pooled univariate results were used to provide a more sensitive test, but if $p < 0.2$, a multivariate test which gave more robust results was used.

Accuracy of the pharmacokinetic model controlled infusion of propofol was performed using the methods and terminology previously described [Marsh *et al* , 1991] to allow direct comparison of results. Predicted error was defined as

$$\text{Predicted error} = \frac{\text{Cp (measured) - Cp (predicted)}}{\text{Cp (predicted)}} \times 100\%$$

where Cp = plasma concentration of propofol. Bias was defined as the mean prediction error. Precision was defined as the mean of the sum of the absolute values of prediction error and it is a measure of the degree of scatter of the data about the line of perfect prediction. The least mean square error was estimated and this was used to update the individual sets of

pharmacokinetic parameters to improve the prediction accuracy of the pharmacokinetic model.

All statistical analyses were performed on personal computers (Macintosh II si, (Apple computer, Inc, California, USA), and IBM compatible PC computers) and the IBM 4381 computer at the Computer Centre, the Chinese University of Hong Kong. Statistical packages used were Statview II (Abacus Concepts Inc, Berkeley, USA), SPSS-PC and SPSS-X (SPSS Ltd,. Chicago, Illinois, USA), SAS (SAS Institute Inc, Cary, NC,USA) and BMDP (BMDP Statistical Software Inc, Los Angeles, CA, USA). Patient raw data are presented in Appendix C (page 192).

SECTION III
INDUCTION OF ANAESTHESIA

CHAPTER 3

Induction Dose Requirement

INDUCTION DOSE REQUIREMENT

Introduction

It is well recognised that the body size and composition of children change throughout childhood [Friis-Hansen, 1961], and these changes by affecting pharmacokinetics may influence the dose requirement in clinical practice [Morselli, Franco-Morselli, and Bossi, 1980; Booker, 1989].

Studies have observed that children require a larger dose of propofol for induction of anaesthesia than adult patients [Purcell-Jones *et al*, 1987; Morton *et al*, 1988; Mirakhur, 1988, Valtonen *et al* 1988]. Two previous dose-response studies have shown that children require a larger dose of propofol for induction of anaesthesia than adults [Patel *et al*, 1988; Hannallah *et al*, 1991]. The data in these studies were not subdivided into different age groups. Growth and development is a continuous process throughout childhood, and could affect the dose requirement at different ages during this period. This part of the study was designed to determine the induction dose of propofol using a quantal dose-response method in unpremedicated Chinese children of three different age groups.

Methods

This part of the study was performed on 300 healthy Chinese children (ASA I and II) aged between six months and 12 years who were scheduled for elective minor surgery. Children, who were grossly obese, with a known history of allergy or of any adverse reactions to anaesthesia were excluded from the study. For this study, obesity was defined as body weight in excess of the 97th percentile for the corresponding age taken from the standard chart for Chinese children [Lau *et al*, 1987, Leung *et al*, 1988]

Preoperative preparation included EMLA emulsion cream applied to the dorsum of both hands and it was covered with an impervious dressing about an hour before anaesthesia. The children were divided according to their age into three groups, group A (less than 2 years), group B (2 - 5 years), and group C (6 - 12 years). Patients in each group were allocated to receive one of eight doses of propofol from coded envelopes in a randomised double-blind manner. The eight doses of propofol were 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, and 2.6 $mg.kg^{-1}$.

The selected dose of propofol was injected intravenously over approximately 20 seconds through a 24 SWG cannula. Lignocaine 0.05 ml of 1% was added to each millilitre of 1% propofol emulsion immediately before administration. This was the same dosage used by Patel and colleagues [1988] and by Brooker and Redfern [Brooker, Hull, and Stafford, 1985; Redfern, Stafford MA, Hull CJ. 1985; Brooker, Redfern 1986]. Twenty seconds after completion of the propofol injection, the adequacy of induction was assessed by evaluating the patient's responses to brushing of the eyelashes (LER), and to the gentle application of a facemask (AFM) delivering 0.5% halothane and 70% nitrous oxide in oxygen. After this assessment, anaesthesia was continued as required

either by increasing the concentration of halothane or giving an incremental dose of propofol. Systemic arterial pressure and pulse rate were monitored throughout the procedure using a noninvasive automatic blood pressure monitor. An oximeter was used to monitor oxygen saturation. Pain on injection, apnoea and other side effects were noted. In older children, verbal complaint of pain or withdrawal of the arm in which the drug was injected, were taken to indicate pain, whereas in children less than three years old, grimacing, crying or a withdrawal response were taken as an indication of pain.

Effective dose response curves for loss of eyelash reflex (LER) and acceptance of facemask (AFM) for 50% (ED_{50}) and 95% (ED_{95}) in the three age groups were calculated and plotted using probit analysis as described in the methods chapter (page 48). The fitting of the probit curves to the raw values was assessed by Pearson's goodness-of-fit test. The differences between the dose response curves were analysed using the chi-square parallelism test. The differences between the effective doses of the three groups were tested by the t-test with Bonferroni adjustment using the software package Statistical Package for Social Sciences version 3.1. The adjustment was to limit the total probability of error committed in performing these tests to below 0.05. Chi-square tests were used to test for any association between dosage and the incidence of side effects.

Results

Of the three hundred children in the study, 48 were in group A (less than 2 years), 117 in Group B (2-5 years) and 135 in Group C (6-12 year). Patients' details and the proportion in each age and dose group who demonstrated absence of eyelash reflex and acceptance of the facemask are shown in Table 3.1. Individual demographic data are listed in Appendix C (page 194). There were more boys than girls in the sample. This reflects the predominance of male genital procedures in minor paediatric surgery in the Prince of Wales Hospital, Shatin.

TABLE 3.1. *Details of patients in each dose group (mean (SD) and numbers who demonstrated loss of eyelash reflex (LER) and acceptance of facemask (AFM). (From Aun et al, 1992).*

	Dose $mg.kg^{-1}$	Number of patients	Age (yr) Mean (SD)	Body Wt (kg) Mean(SD)	Sex M:F	LER (%)	AFM (%)
Group A	1.2	4	1.2 (0.3)	10.3 (1.5)	4:0	0	0
(< 2 yr)	1.4	3	1.0 (0.1)	10.4 (2.4)	2:1	0	0
	1.6	7	1.2 (0.3)	9.3 (1.3)	6:1	0	0
	1.8	6	1.4 (0.4)	10.5 (0.9)	5:1	66	50
	2.0	8	1.4 (0.2)	10.4 (1.6)	7:1	75	75
	2.2	7	1.4 (0.2)	9.9 (0.8)	5:2	100	71
	2.4	7	1.2 (0.4)	9.9 (2.0)	6:1	85	86
	2.6	6	1.4 (0.4)	10.0 (0.9)	4:2	100	100
Group B	1.2	11	4.5 (0.9)	15.3 (2.9)	10:1	18	27
(2-5 yr)	1.4	13	3.9 (0.9)	16.5 (2.7)	10:3	38	23
	1.6	18	4.1 (1.2)	16.2 (3.8)	13:5	39	33
	1.8	12	3.7 (1.1)	14.3 (2.7)	12:0	58	67
	2.0	19	3.8 (1.3)	15.6 (3.2)	17:2	95	95
	2.2	14	3.7 (1.3)	14.8 (2.3)	10:4	86	71
	2.4	17	3.8 (1.5)	15.7 (3.1)	12:5	100	88
	2.6	13	3.6 (1.2)	16.2 (2.7)	10:3	100	92
Group C	1.2	15	8.5 (1.9)	26.3 (7.5)	11:4	40	20
(6-12 yr)	1.4	13	8.1 (1.8)	25.5 (7.2)	11:2	31	38
	1.6	20	8.9 (1.8)	28.2 (8.5)	19:1	70	65
	1.8	17	8.9 (2.0)	27.4 (7.9)	15:2	71	88
	2.0	18	8.5 (1.9)	25.4 (7.1)	11:7	94	100
	2.2	17	8.7 (1.6)	27.6 (8.3)	14:3	88	88
	2.4	18	8.5 (1.8)	24.9 (7.5)	11:7	100	94
	2.6	17	8.6 (1.9)	28.0 (6.0)	13:4	100	100

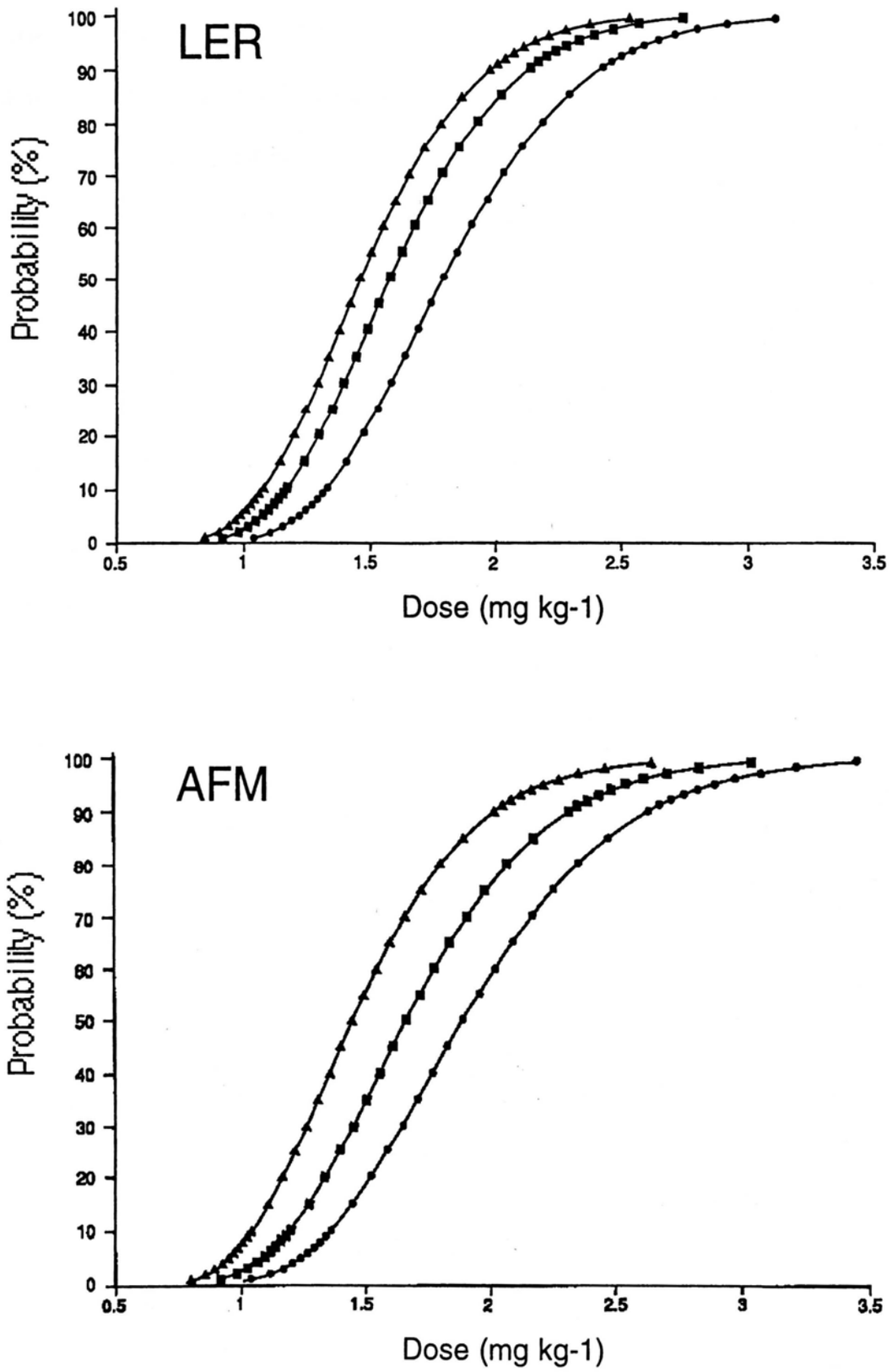


FIGURE 3.1. Dose-response curves for loss of eyelash reflex (LER) and acceptance of facemask (AFM) in group A (●), group B (■) and group C (▲). Probability is the probability of response. (From Aun *et al*, 1992).

The dose response curves for the LER and AFM in the three groups are shown in Figure 3.1. P- values for Pearson goodness of fit test for LER and AFM were 0.327 and 0.355, respectively which suggest that the dose-response curves fit the data well. The ED_{50} and ED_{95} for both the LER and AFM were greatest in group A, less in group B and smallest in group C (Table 3.2).

TABLE 3.2. *Estimated dose of propofol ($mg.kg^{-1}$) that is required to induce loss of eyelash reflex and acceptance of facemask in 50% and 95% of children (mean with 95% confidence intervals). (from Aun et al, 1992).*

	Group A (< 2 years)	Group B (2-5 years)	Group C (6-12 years)
Loss of eyelash reflex			
ED_{50}	1.79 (1.61 - 1.97)	1.58 (1.46 - 1.69)	1.46 (1.35 - 1.56)
ED_{95}	2.63 (2.36 - 3.02)	2.32 (2.14 - 2.59)	2.14 (1.98 - 2.38)
Acceptance of facemask			
ED_{50}	1.88 (1.69 - 2.09)	1.66 (1.53 - 1.77)	1.44 (1.32 - 1.55)
ED_{95}	2.88 (2.55 - 3.36)	2.53 (2.31 - 2.86)	2.20 (2.02 - 2.46)

For both endpoints, the differences in ED_{50} and ED_{95} between groups A and C were statistically significant, whereas those between groups A and B were not. However, between groups B and C, a significant difference was observed in AFM but not in LER suggesting that LER is a less sensitive indicator than AFM. The relatively small number of patients in group A may have contributed to the difference in either LER

or AFM between groups A and B not being significant as there were relatively fewer suitable patients in those less than 2 years old. The dose requirements to achieve AFM were larger than those for LER in all three groups although the differences were not statistically significant (Figure 3.2) .

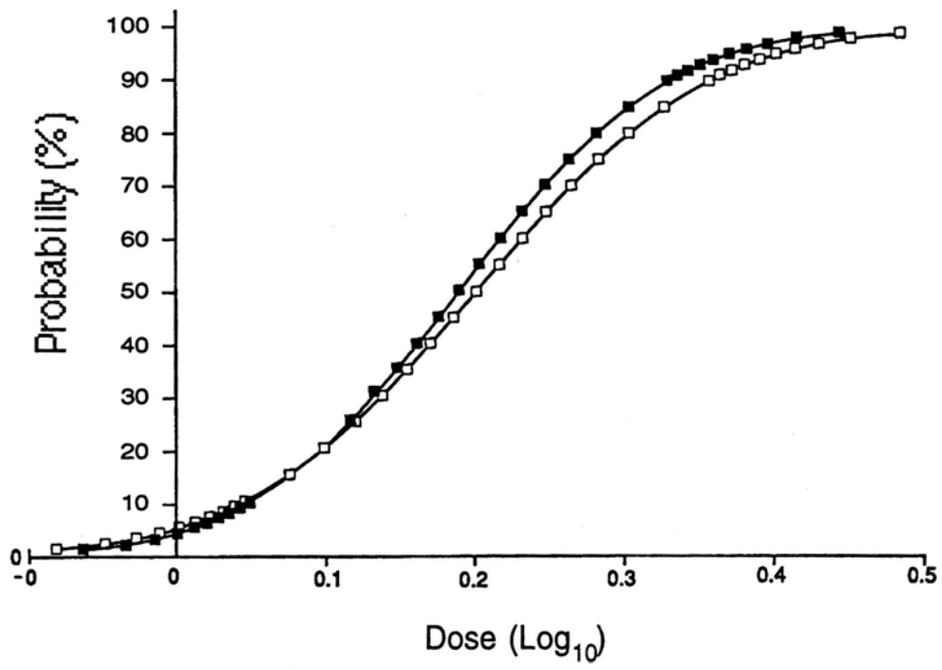


FIGURE 3.2. Dose response curves of LER (■) and AFM (❑) for all patients as a group (n=300).

The p values of chi squared parallelism analysis of the dose response curves for both LER and AFM were not significant throughout the dose range (0.346 and 0.161, respectively). This demonstrates that the three curves were "parallel" which implies that a constant ratio between them can be deduced. If group C (with the smallest ED dose) is taken as the reference, the relative ratios of dose-response for LER were 1.3 and 1.2 for group A and B, respectively; those for AFM were 1.2 and 1.1 for group A and B, respectively.

The incidences of apnoea greater than 20 seconds duration were 0 - 28.6% in group A, 0 - 42.1% in group B and 5.9 - 52.9% in group C (Figure 3.3). They were dose-related ($p < 0.001$). The apnoeic episodes, however, resolved spontaneously and did not interfere with the continuation of anaesthesia.

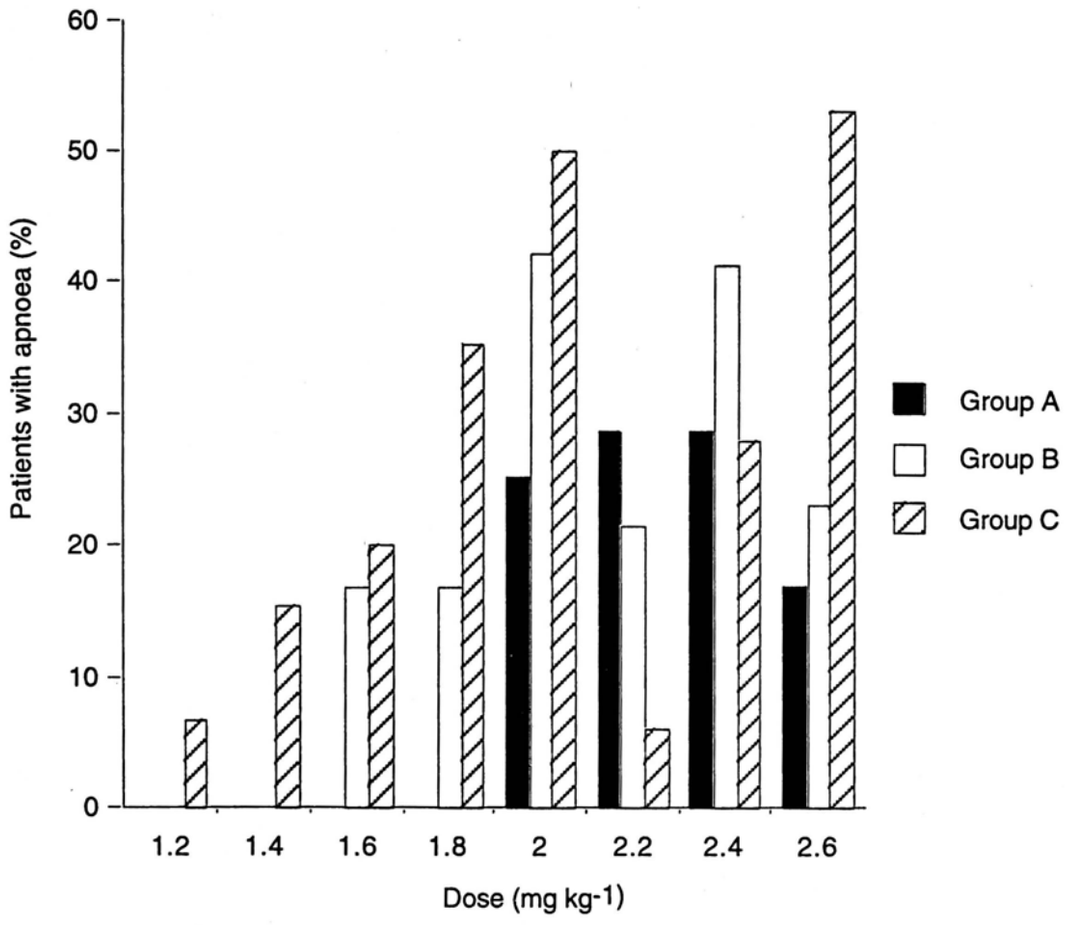


FIGURE 3.3. Incidence of apnoea ≥ 20 s in the three groups of patients. (From Aun *et al*, 1992).

The incidences of pain were 0 - 42.9% in group A, 9.1 - 33.3% in group B, and 7.7 - 35.3% in group C (Figure 3.4). They were not dose-related ($p = 0.47$). Involuntary movements were observed in 43.8% in group A, 54.7% in group B and 47.4% in group C.

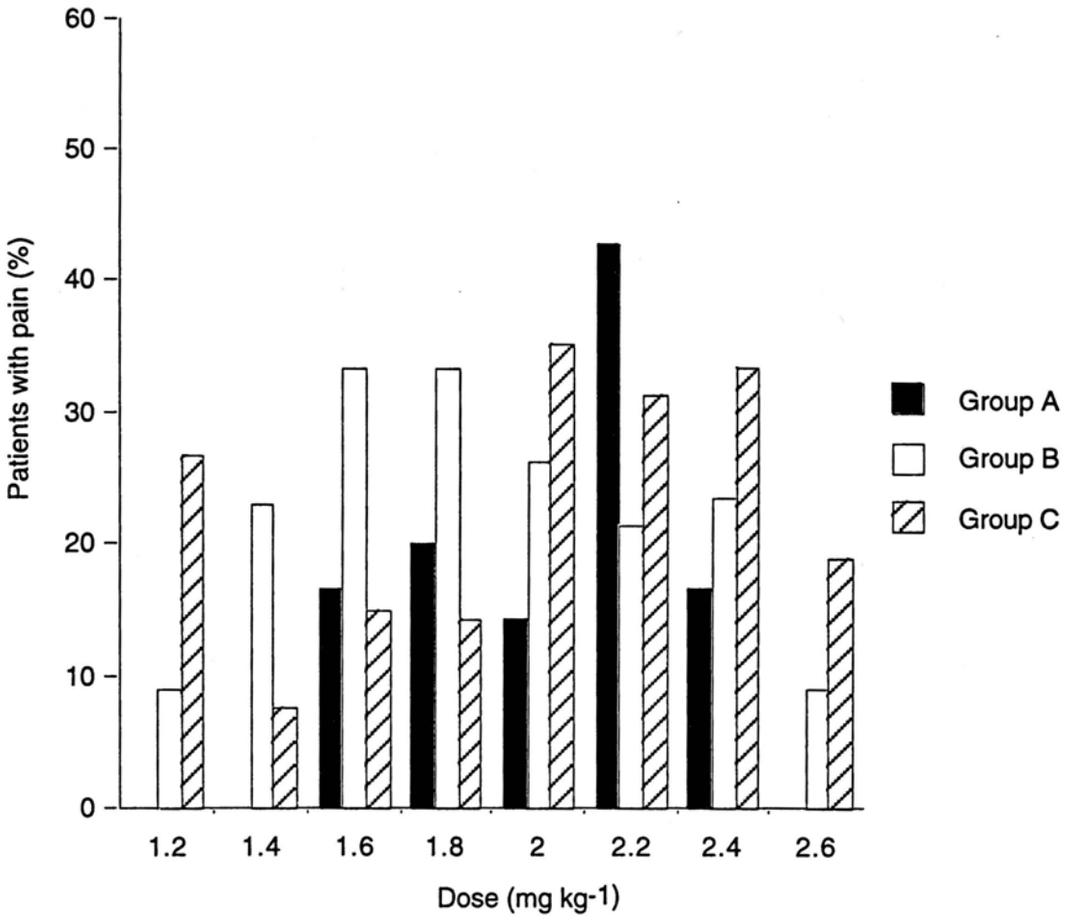


FIGURE 3.4. Incidence of pain on injection in the three groups of patients. (From Aun *et al*, 1992).

In this study, the mean arterial pressures decreased in all three groups. At two minutes after propofol, the reduction was greatest in group A (28.7%), less in group B (23.5%) and least in group C (18.0%). The pulse rate was relatively stable in group C (+ 1.4%), but decreased in groups A (-15.5%) and B (-12.2%) (Table 3.3).

TABLE 3.3. *Mean (%) changes in mean arterial pressure (MAP) and pulse rate (PR) at 1 minute and two minutes after propofol administration.*

	MAP (mmHg)			PR (bpm)		
	BL	1 min	2 min	BL	1 min	2 min
Group A (< 2 yr)	89.6	70.0 (-21.9%)	63.9 (-28.7%)	145.0	122.0 (-15.9%)	122.5 (-15.5%)
Group B (2-5 yr)	85.4	71.7 (-16.0%)	65.3 (-23.5%)	112.0	107.0 (-4.5%)	99.8 (-12.2%)
Group C (6-12 yr)	83.2	73.9 (-11.2%)	68.2 (-18.0%)	89.9	98.3 (+9.3%)	91.2 (+1.4%)

Discussion

Grossly obese children were excluded from the study, because their differences in body composition from their average counterparts may have a different dose requirement.

The dose requirements for accepting facemask (AFM) is larger than those for loss of the eyelash reflex (LER) in all three age groups suggesting that the acceptance of a facemask occurred at a deeper plane of anaesthesia

than did the loss of the eyelash reflex. This is similar to the findings in other anaesthetic quantal dose-response studies in children [Coté *et al*, 1981; Patel *et al*, 1988]. In a multicentre propofol dose-finding study in adults [Cummings *et al*, 1984], three indicators were used to assess the success of induction. They were 1) cessation of counting, 2) loss of eyelash reflex and 3) dropping of a water filled 20 ml syringe held by the nozzle between the tips of the thumb and index finger with the arm extended. Loss of eyelash reflex was found to be the least reliable sign. However, the other two methods need cooperation from patients and are impractical in children. The acceptance of the facemask was considered to be a satisfactory endpoint, as in clinical practice, this criterion is usually used as an indicator of smooth transition to maintenance of anaesthesia with inhalational agents [Coté *et al*, 1981; Patel *et al*, 1988].

The ED_{50} and ED_{95} doses for both LER and AFM were greatest in children less than two years old, less in those between two and five years, and least in children above six years old. Hannallah and colleagues [1991] did not find any age-related differences in dose requirements and therefore they analysed their data in one group. However, a similar trend of differences has been observed in other studies [Morton *et al*, 1988; Westrin, 1991; Manschot *et al*, 1992]. The children studied were of a slightly different age range, and the methods for estimating the effective dose were also different. Morton used a titration method comparing children between one and five with those between five and 10 years old; Westrin used an up and down method to compare infants one to six months old with children 10-16 years old; and Manschot and colleagues [1992] compared the proportions of patients that were successfully induced in three age groups of children, three to five years, six to nine years and 10-15 years old. All these studies confirmed that younger children require a larger dose of propofol than older children and adults.

This may be attributed to differences in pharmacokinetics and pharmacodynamics between different age groups of children.

The data from the current study was combined according to the corresponding age groups as in the studies by Patel and colleagues [1988] and Hannallah and colleagues [1991] for comparison (Table 3.4).

TABLE 3.4. *Comparison of effective dose values of propofol in children.*

	LER		AFM	
	ED_{50}	ED95	ED50	ED95
Patel (1988) (1-12 yr)	1.6 (1.2- 1.9)	2.8 (2.3- 3.5)	2.5 (2.1-3.0)	5.2 (4.1-8.1)
Aun (1-12 yr)	1.54 (1.5-1.6)	2.28 (2.2-2.5)	1.59 (1.4-1.7)	2.44(2.2-2.9)

	(LER plus AFM)	
Hannallah (1991)	ED50	ED95
(3-12 yr)	1.5 (1.3-1.7)	2.3 (2.1-3.0)
Aun (2-12 yr)	1.59 (1.39-1.74)	2.44 (2.15- 3.16)

The ED doses in children two to 12 years old in this study were similar to those in Hannallah's study. A two sample t-test was performed which confirmed that there was no significant difference between the results of the two studies ($p=0.6$). However, the lack of age-related difference in requirements in their study may be due their small sample size studied. In the study by Patel, the ED doses in the unpremedicated children are larger than in the current study. This may be related to both their small number of patients, and the use of extrapolation to determine some values.

Allowing for these differences in methodologies, there is a general agreement that healthy children require a larger dose of propofol than adult patients. It is therefore recommended that, doses in the range of 2.5 - 3.5 $mg.kg^{-1}$ are required for induction of anaesthesia in healthy unpremedicated children. In pracrice, the dose should be given by titration. The lower dose range is more suitable for older children and the higher range in younger children. Children with premedication should need less [Patel *et al*, 1988].

Apnoea occurs more frequently in older children (see Figure 3.3) suggesting that either this side effect is age-dependent or that propofol is more sensitive in older children. This finding confirms that of two other studies [Valtonen *et al*, 1988; Manschot *et al*, 1992].

The incidence of pain on injection in this study ranged from 0-42.9%. The wider range observed in group A suggested that it is difficult to assess pain in children around one to two years old. The range in group B and C are more consistent. The dose of lignocaine used was 0.15 mg per 3 mg of propofol which is the same as the dose used by Morton and colleagues [1988] and Patel and colleagues [1988]. The incidence obtained in the current series is on average similar to their incidences. However, Morton [1990] subsequently showed that 1 mg of lignocaine per 3 mg propofol abolished injection pain in the veins of the dorsum of the hand in unpremedicated children. The minimum effective dose of lignocaine required to prevent pain in children was suggested to be 0.2 $mg.kg^{-1}$ [Morton *et al*, 1992].

The reduction in arterial pressure and pulse rate were more pronounced in the younger age groups. This finding therefore needs further evaluation.

The incidence of involuntary movements after propofol has been very variable in the literature depending on how closely the investigators

looked for them [Borgeat *et al*, 1993]. The high incidence of involuntary movements observed in this study was similar to those reported by others [Purcell-Jones *et al*, 1985; Borgeat *et al*, 1991]. They were short lived and did not disrupt the conduct of anaesthesia and surgery. The origin of this side effects remains unclear. It has been shown that the frequency of these movements can be reduced by a slightly larger dose of propofol [Borgeat *et al*, 1991] or administration of nalbuphine [Borgeat *et al* 1993].

In summary, healthy children required a larger dose of propofol than adult patients. The dose of propofol required for induction of anaesthesia in unpremedicated children is in the range of 2.5-3.5 $mg.kg^{-1}$. The lower range is for older children and the higher range for younger children.

CHAPTER 4

Influence of Propofol Dose on Haemodynamic Changes

INFLUENCE OF PROPOFOL DOSE ON HAEMODYNAMIC CHANGES

Introduction

A significant reduction in arterial pressure usually follows the induction of anaesthesia with a bolus dose of propofol in both adults [Fahy, van Mourik, and Utting, 1985; Grounds *et al*, 1985; McCollum and Dundee, 1986; Coley *et al*, 1989] and in children [Purcell-Jones *et al*, 1987; Mirakhur, 1988; Valtonen *et al*, 1988; Morton *et al*, 1988; Hannallah *et al*, 1991]. Children require a larger dose of propofol for induction of anaesthesia than adults. It is possible that this increased dose requirement may have a dose-related effect on haemodynamic changes. To test this hypothesis, the haemodynamic changes after different doses of propofol were examined.

Methods

Two hundred and sixteen children from the study in Chapter 3 were selected for this study. A stratified random allocation was used to divide the children into six groups depending on the dose of propofol received. These were 1.6, 1.8, 2.0, 2.2, 2.4, or 2.6 $mg.kg^{-1}$. Those who received less than 1.6 $mg.kg^{-1}$ were not included in this study, as the doses were too small. Such data may not be clinically relevant. Children with a known history of allergy or adverse reaction to previous anaesthesia were excluded from the study. All children had EMLA cream applied to the dorsum of both hands approximately one hour

before the estimated time of anaesthesia. No other premedicant was used. On arrival in the anaesthetic room, a noninvasive automatic blood pressure monitor was applied to one arm and a 24-gauge cannula was inserted intravenously into the other hand, which also had an oximeter probe attached to monitor the oxygen saturation. The child was allowed to settle and a baseline arterial pressure reading was taken. Following this, the predetermined dose of propofol was given over a period of approximately 20 seconds. One percent lignocaine 0.05 ml was added to each millilitre of propofol immediately before administration. The 'Dinamap' was programmed to cycle every minute and the arterial pressure and pulse rate were recorded on the attached printer. After assessment of the response to gentle application of a face mask, the patient was allowed to breathe a mixture of nitrous oxide 70% and halothane 0.5% in oxygen spontaneously through a modified Ayre's T-piece. The child was not disturbed during the study period of five minutes, to avoid producing haemodynamic changes. Pain on injection was assessed by the reaction of the child during administration of the drug. In older children, the spontaneous complaint of pain or a withdrawal response was taken as indication of pain. For children under three years of age, grimacing, a cry on induction, or a withdrawal response was used instead. The attitude (anxious or calm) of the patient before induction was also noted.

Statistical Analysis

The demographic data were compared using analysis of variance and chi-square test. Blood pressure and pulse rate changes were analysed by a multivariate analysis of variance for repeated measures.

Results

Data from three patients were incomplete and therefore excluded from the analysis. The demographic details of the six dose groups are shown in Table 4.1. There were no statistically significant differences between age, weight, and sex of the children in any of the dose groups.

TABLE 4.1. *Mean and standard deviation (SD) of age (years) and weight (kg) of patients in the six dose groups.*

Propofol dose (mg. kg^{-1})	1.6	1.8	2.0	2.2	2.4	2.6
Number (n)	34	34	37	35	41	32
Age (yr) mean (SD)	5.7 (3.4)	5.6 (3.5)	5.4 (3.2)	5.2 (3.2)	5.0 (3.3)	4.9 (3.2)
Wt (kg) mean (SD)	21.7 (10.3)	20.3 (9.2)	19.5 (7.9)	19.7 (8.9)	18.6 (7.8)	19.7 (7.8)
Sex (M/F)	29/5	32/2	27/10	27/8	28/13	25/7

The preoperative arterial pressures and pulse rates were similar in all the dose groups. The mean values of systolic, diastolic, and mean arterial pressures decreased significantly following induction in all six groups ($p < 0.001$). The changes in arterial pressures and pulse rate of individual patients are listed in Appendix C (page 199). The changes in mean arterial pressures for individual groups over the five minutes following induction is shown in Figure 4.1. The mean reduction in mean arterial pressure was approximately 15% over the first minute and approximately 30% at five minutes after propofol. However, there was no difference between the six dose groups at any given time (between-

group effect), [p values were 0.3, 0.6, and 0.9 for systolic, mean, and diastolic arterial pressures respectively]. There was also no significant difference in the rates of reduction in arterial pressure between the dose groups (group-time interaction) [p values were 0.8, 0.8, and 1.0 for systolic, mean, and diastolic arterial pressures respectively].

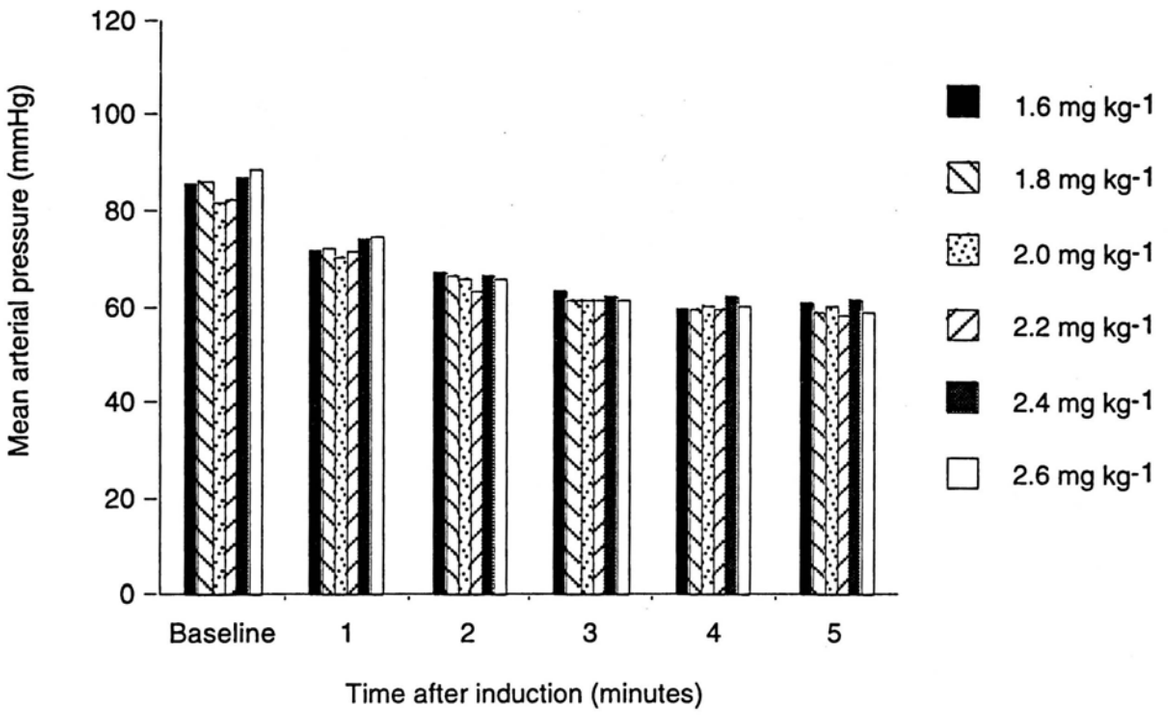


FIGURE 4.1. Changes in mean arterial pressure following propofol. Mean values for each dose group. There was no difference between the groups at any given time. The rate of reduction was not different (From Short and Aun, 1991)

Changes in pulse rate showed a similar trend to that of the arterial pressures (Figure 4.2). There was a significant reduction in mean pulse rate of 17% over the five minutes following induction, although there was no differences between dose groups [p = 0.5 for between-group effect, 0.7 for group-time interaction].

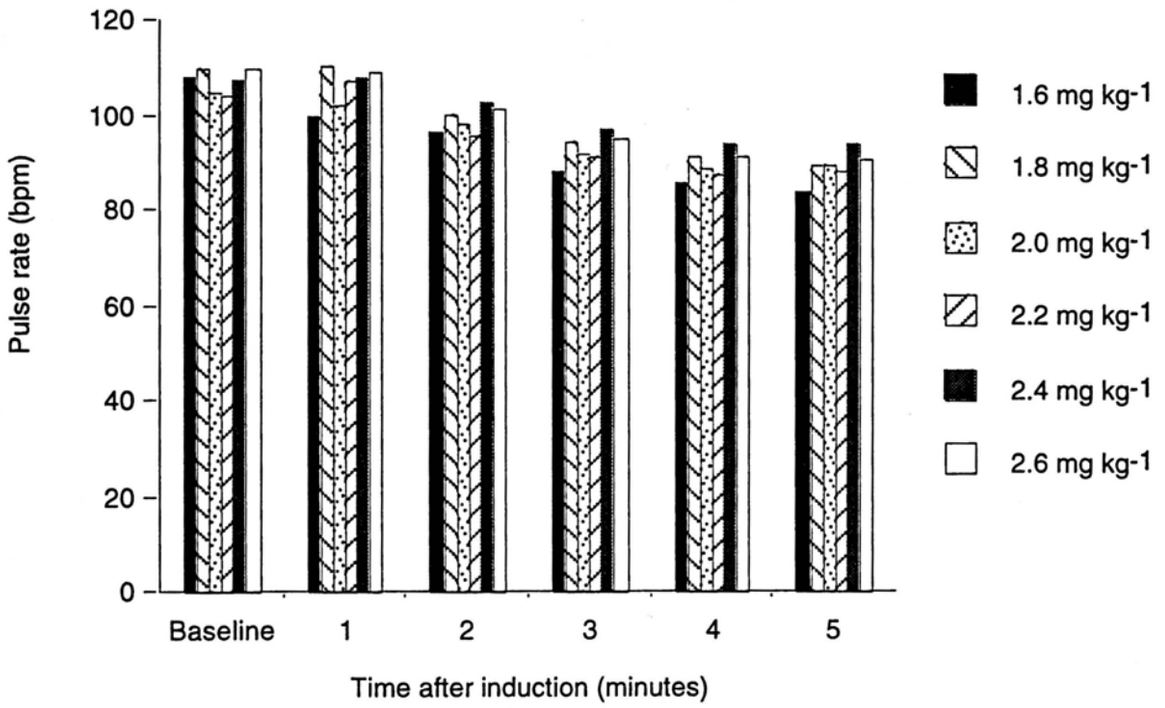


FIGURE 4.2. Changes in mean pulse rate following propofol. Mean values for each group. There was no difference between the groups at any given time. The rate of reduction was not different (From Short and Aun, 1991)

Thirty four percent of children appeared anxious before induction. The incidence of pain on injection was 24.1%. There was no significant difference in the incidence of anxiety or pain between the dose groups.

Discussion

In an adult study, a dose-related decrease in arterial pressure and an increase in pulse rate were observed [Major *et al*, 1981]. However, in the current study, the reductions in arterial pressures and pulse rates following propofol induction in children were not dose-related. The dose range used by Major and colleagues is similar to this study. A recent study on the dose of propofol required in children between three and 15 years old produced similar findings [Manschot *et al*, 1992]. The reason for this difference in response between adults and children is not clear. The propofol used in the adult study [Major *et al*, 1981] was the old formulation in Cremophor, whereas the new emulsion formulation was used by Manschot and colleagues and in the current study. However, the difference is unlikely to be due to the use of different formulations of propofol used, as Glen and Hunter [1984] have shown similar anaesthetic and haemodynamic effects with both formulations.

The magnitude of reduction in arterial pressure after propofol was similar to that of adults [Grounds *et al*, 1985]. The reduction in pulse rate was greater than that in adults suggesting that the baroreflex is impaired more in children. However, it was not dose-related within the dose range studied (1.6 to 2.6 $mg.kg^{-1}$). In contrast, Major and colleagues [1981] observed a dose-related initial rise in pulse rate and attributed this to the pain associated with propofol administration (80% when a small vein on the dorsum of the hand was used). The reason for the lack of tachycardia in this study is not clear. The pain incidence (24%) was lower than that observed by Major and colleagues [1981].

The inclusion of inhalational agents (nitrous oxide and halothane) in the study may be criticised. Both agents are known to influence haemodynamics but inhalational agents were necessary to

allow the cardiovascular monitoring. However such a technique may reflect more accurately the haemodynamic changes which occur in clinical practice.

In children, because of ethical and technical constraints, invasive monitoring was not used. Instead, Doppler echocardiography was used, the results of which are presented in Chapter 5.

In summary, induction of anaesthesia with propofol in children produces a reduction in arterial pressure and pulse rate. These changes were not dose-related.

CHAPTER 5

Comparison of Cardiovascular Effects of Propofol and Thiopentone

COMPARISON OF CARDIOVASCULAR EFFECTS OF PROPOFOL AND THIOPENTONE

Introduction

Induction of anaesthesia with propofol caused a significant reduction in arterial pressures which was greater than that after thiopentone both in adults [Grounds *et al*, 1985; Fahy, van Mourik, and Utting, 1985; McCollum and Dundee, 1986; Lippman *et al*, 1988; Coley *et al*, 1989] and in children [Purcell-Jones *et al*, 1987; Valtonen *et al*, 1988; Morton *et al*, 1988].

In adults, the mechanisms of hypotension have been studied extensively by the invasive dye and thermodilution method [Grounds *et al*, 1985; Coates *et al*, 1987; Monk *et al*, 1987; Claeys, Gepts, and Camu, 1988; Lippmann *et al*, 1988] and the Doppler echocardiographic method [Fairfield, Dritsas, and Beale, 1991; Gauss *et al*, 1991]. In adult studies, the cardiovascular effects of propofol have been controversial. Decreases in cardiac output [Monk *et al*, 1987; Lippmann *et al*, 1988], decreases in systemic vascular resistance (SVR) [Claeys, Gepts, and Camu, 1988] or both [Grounds *et al*, 1985; Coates *et al*, 1987; Gauss *et al*, 1991] have been reported. Fairfield, Dritsas, and Beale [1991] suggested that the conflict in the results was due to a biphasic effect of propofol on the cardiovascular system.

In children, the haemodynamic data are limited to noninvasive measurements of arterial pressure and heart rate and these are inadequate to describe the cardiovascular effects of anaesthetic agents [Wolf, Neal, and Peterson, 1986]. This study compared the cardiovascular effects of propofol with that of thiopentone in Chinese children using the

technique of pulsed-Doppler echocardiography. The accuracy and application of this method in paediatric patients has been described in Chapter 2 (page 34).

Methods

This study was performed on 45 healthy Chinese children aged between eight months and 12 years (ASA I or II) and scheduled for elective surgery. Children with a history of allergy, or of any adverse reactions to previous anaesthesia were excluded from the study. Those children in whom pre-induction haemodynamic variables or venous access could not be obtained were withdrawn from the study. All patients were premedicated with oral diazepam syrup 0.4 $mg.kg^{-1}$ and EMLA cream was applied to the dorsum of both hands approximately two hours before anaesthesia. The children were grouped into two age groups, less than two years old and between two and 12 years old. Children in each age group were then allocated randomly in a double-blind manner to receive either propofol 2.5 $mg.kg^{-1}$ or thiopentone 5 $mg.kg^{-1}$.

On arrival in the anaesthetic room, a noninvasive automatic blood pressure monitor was applied to one arm, and a 24-gauge intravenous cannula was then inserted into the opposite hand, where an oximeter probe was also attached for continuous monitoring of arterial oxygen saturation. The child was allowed to settle and the baseline haemodynamic measurements were obtained. The child was noted to be either calm or agitated at this stage. After the baseline recordings, the appropriate intravenous agent was injected over a period of 20 seconds. One percent lignocaine 0.05 ml was added to each millilitre of propofol immediately before administration. As soon as the child was asleep, a face mask was applied and anaesthesia maintained with 70% nitrous

oxide and 0.5% halothane in oxygen using the Jackson-Rees modification of Ayres T piece. Haemodynamic variables were then monitored at one minute intervals for five minutes from the end of the intravenous injection. End-tidal carbon dioxide concentration was monitored using a mainstream capnometer (HP 78356A, Hewlett Packard, California, USA) attached to the face mask. Fresh gas flow was adjusted and ventilation assisted if necessary to maintain end tidal carbon dioxide concentration between 4.7 - 6.0 kPa. After five minutes, the study was concluded, and anaesthesia and surgery proceeded as normal.

Arterial pressures and heart rate were recorded by a 'Dinamap'. Stroke volume was obtained by an ultrasound scanning device (Aloka-280, Aloka Co., Ltd., Tokyo, Japan) using a handheld Doppler probe of 5-MHz. The measurement of stroke volume (SV), calculation of cardiac output (CO), stroke volume index (SVI), cardiac index (CI) and systemic vascular resistance (SVR) have been described in Chapter 2 (page 35).

Statistical Analysis

In order to study and compare the effects of two agents in two age groups of children, the patients were divided into four groups for statistical analysis. They were:

Group I, infants less than two years old who received propofol;

Group II, infants less than two years old who received thiopentone;

Group III, children between two and 12 years who received propofol and

Group IV, children between two and 12 years who received thiopentone.

Patients' data between the same age groups were compared using a two-tailed Student's *t* test. The number of agitated children and the incidence of side effects were analysed by chi-square test. The baseline haemodynamic variables were compared by one way analysis of variance. The haemodynamic measurements after induction were analysed using

repeated measures analysis of variance for the differences from the baseline values. The factors included were time after induction, anaesthetic agents, and age interaction. In the absence of statistically significant age by anaesthetic agent interactions, data from the four groups were compared simultaneously in the results.

Results

Four cases were excluded from the analysis because of their inadequate Doppler recordings. Of the 41 patients studied, 18 were infants (9 in group I, 9 in group II), and 23 were older children (12 in group III and 11 in group IV). Patient data and the ratio of agitated to calm children in each group are listed in Table 5. 1. Individual data are listed in Appendix C (page 204).

There were no statistically significant differences in the mean age, body weight and surface area between group I and II or between group III and IV. In groups III and IV, there were more girls. There were more anxious children ($P = 0.01$) in groups I and II when compared with groups III and IV (Table 5. 1).

TABLE 5.1. *Patient demographic data (mean (SD)).*

BSA = body surface area. Mood (a:c) = number of agitated to calm children

	Group I (n = 9)	Group II (n = 9)	Group III (n = 12)	Group IV (n = 11)
Age (yr)	1.2 (0.5)	1.1 (0.4)	5.2 (3.3)	4.4 (2.5)
Sex (m:f)	9:0	7:2	10:2	6: 5
Weight (kg)	10.6 (1.3)	9.7 (1.3)	18.8 (8.5)	16.4 (6.4)
BSA (m^2)	0.46 (0.04)	0.44(0.06)	0.78(0.24)	0.70(0.20)
Mood (a: c)	7:2	5:4	4:8	1:10 *

* ($P<0.05$).

Baseline haemodynamic variables were not significantly different between groups I and II or between groups III and IV (Table 5.2).

The mean heart rates were greater ($P = 0.001$) and systemic vascular resistance values greater ($P = 0.003$) in the infants (groups I and II) than their respective values in the older children (groups III and IV). The differences in the arterial pressures, systemic vascular resistance and cardiac index among the four groups were not statistically significant.

TABLE 5.2. *Measured and derived haemodynamic variables before induction {mean (SEM)}. SAP = systolic pressure, DAP= diastolic pressure, MAP= mean arterial pressure, HR= heart rate, SVI= stroke volume index, CI= cardiac index, SVR= systemic vascular resistance ,*

	Group I (n=9)	Group II (n=9)	Group III (n=12)	Group IV (n=11)
SAP (mmHg)	104.6 (5.3)	104.6 (5.3)	106.7 (5.0)	96.3 (3.9)
DAP (mmHg)	71.6 (3.6)	70.4 (4.6)	67.9 (3.0)	61.2 (3.3)
MAP (mmHg)	85.7 (3.4)	85.3 (5.0)	85.3 (3.8)	75.5 (2.9)
HR (bpm)	162.0 (12.3)	143.7 (10.1)	101.1 (5.7)	102.5 (4.2)**
SVI ($ml.b^{-1}.m^{-2}$)	33.5 (3.8)	34.1 (2.5)	41.7 (1.6)	43.9 (3.8)
CI ($l.\ min^{-1}.m^{-2}$)	5.2 (0.5)	4.9 (0.5)	4.2 (0.2)	4.6 (0.3)
SVR ($dynes.sec.cm^{-5}$)	3129.7 (332.9)	3413.7 (289.6)	2290.6 (186.1)	2203.6 (226.9)*

* $P<0.01$, ** $P<0.001$.

After induction, systolic, mean, and diastolic arterial pressures decreased significantly ($P<0.001$) in all four groups (Figure 5.1). In the infants, the maximum reduction in mean arterial pressure was 31% after propofol (group I) and 21% after thiopentone (group II). In the older children, the maximum reductions were 28% after propofol (group III) and 14% after thiopentone (group IV). For both age groups, the differences were significantly greater after propofol than after thiopentone ($P = 0.011$).

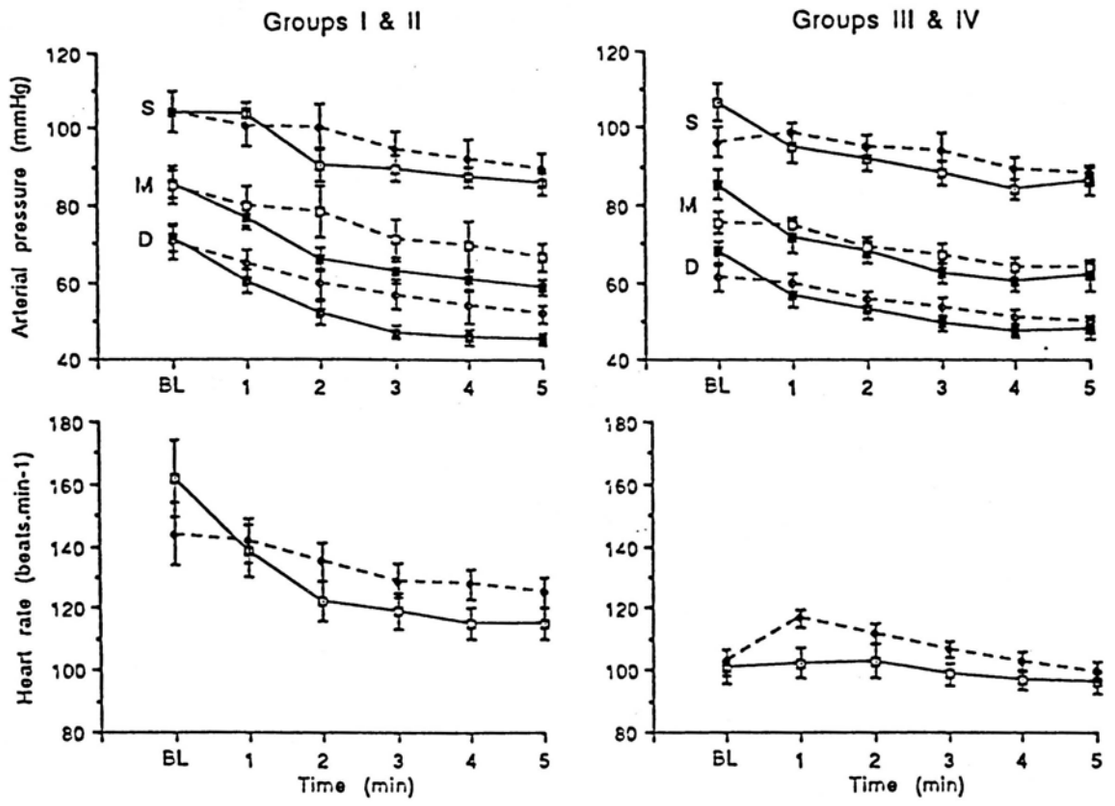


FIGURE 5.1. Changes in arterial pressures and heart rate during induction of anaesthesia. Group I and II - infants less than two years old, group III and IV - children between two and 12 years old. BL = baseline (before induction); Time = time after induction. S = systolic pressure, M = mean arterial pressure, D = diastolic pressure. — = propofol; --- = thiopentone. (From Aun *et al*, 1993)

Heart rate decreased significantly in infants who received propofol (24%), the decrease was significantly more than for those who had thiopentone (11%) ($P = 0.024$). The mean heart rate was stable in the older children who received either propofol (group III) or thiopentone (group IV) (Figure 5.1). There was a significant difference ($P<0.001$) in the magnitude of heart rate changes for the two age groups.

Cardiac index which is a reflection of the combined effects of heart rate and stroke volume index, decreased significantly ($P=0.005$) in all four groups (Figure 5.2). In the infants the maximum decrease in cardiac index was 15% after propofol and 3% after thiopentone. In the older children, the maximum reduction was similar (10%) after each agent.

There was an increase in stroke volume index after induction up to a maximum of 12% in the infants both after propofol (group I) and after thiopentone (group II). In the older children, stroke volume index decreased maximally by 13% after propofol (group III) and 15% after thiopentone (group IV). These changes were not statistically different (Figure 5.2).

Systemic vascular resistance decreased significantly ($P=0.001$) after induction in all four groups (Figure 5.2). The maximum reduction was similar for the infants who received propofol (15%) and those who received thiopentone (16%). The decrease in systemic vascular resistance in older children who received propofol was almost three times as much (19%) as the reduction in children after thiopentone (7%). The differences between the four groups were not significant.

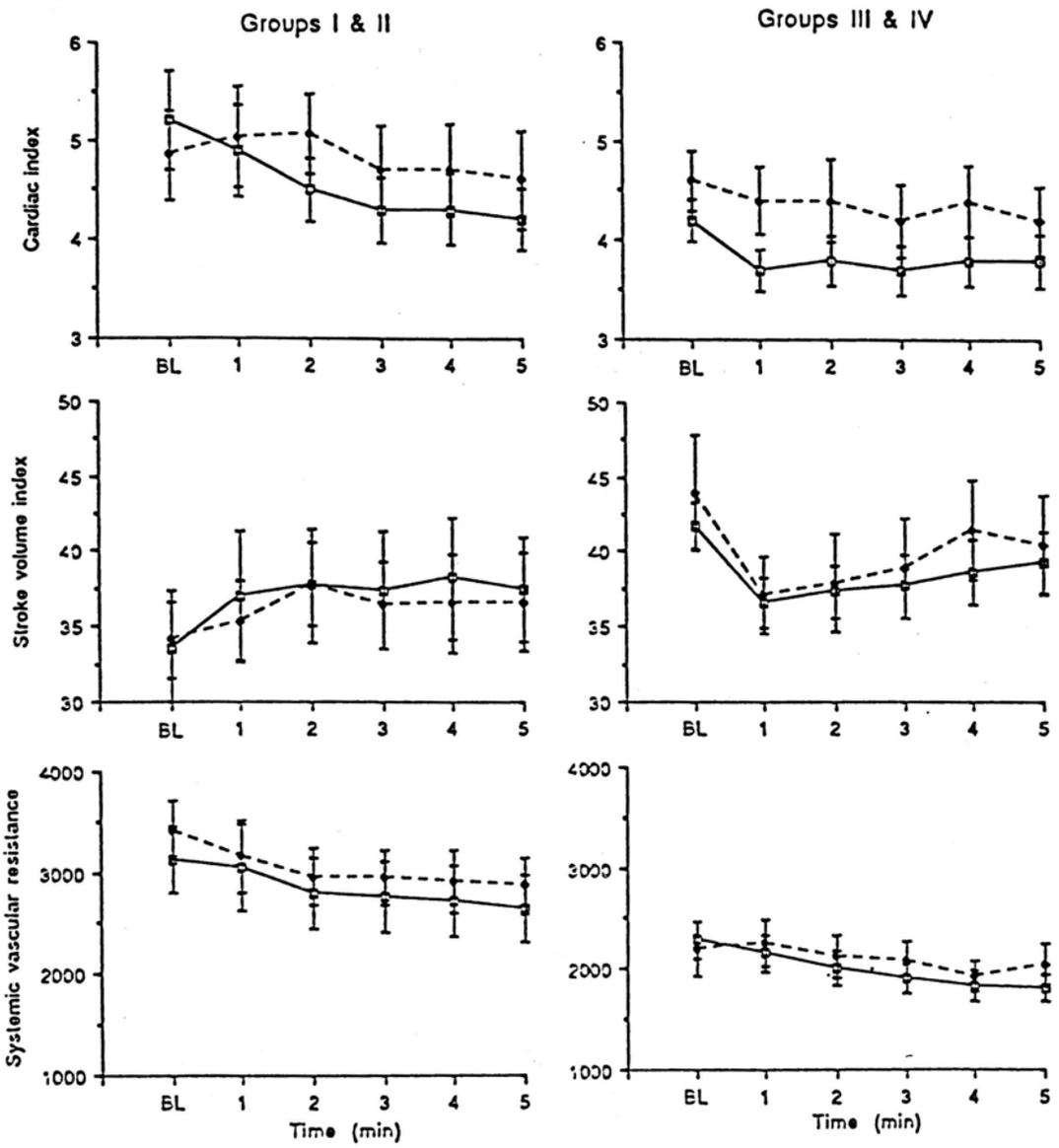


FIGURE 5. 2. Changes in mean cardiac index ($l.min^{-1}.m^{-2}$), mean stroke volume index ($ml.beat.^{-1}m^{-2}$) and mean systemic vascular resistance ($dynes.sec.cm^{-5}$) during induction of anaesthesia. Group I and II - infants less than two years old, group III and IV - children between two and 12 years old. BL = baseline (before induction); Time = time after induction. — = propofol; --- = thiopentone. (After Aun *et al*, 1993)

None of the children showed signs of wakening during the study period. There were no differences between the four groups in the incidence of side effects (Table 5.3).

TABLE 5.3 *Incidence of side effects during induction. (From Aun et al, 1993)*

	Group I n=9	Group II n=9	Group III n=12	Group IV n=11
Pain on injection	2	0	4	1
apnoea > 20 s	5	5	7	5
Movements	1	2	1	0

* $P<0.05$

Discussion

Equipotent doses are required for comparison of cardiovascular responses between two agents. The dose of thiopentone 5 $mg.kg^{-1}$ was chosen as being equipotent to propofol 2.5 $mg.kg^{-1}$. This ratio was based on previous works on their relative potencies [Grounds, Moore, and Morgan, 1986; Leslie and Crankshaw, 1990].

In this study, intravenous induction of anaesthesia in children using propofol was associated with more cardiovascular depression than with an equipotent dose of thiopentone. This is similar to the findings in adults [Grounds *et al*, 1985; Lippmann *et al*, 1988]. The degree of cardiovascular depression in infants was similar to that in older children.

The mean arterial pressure reduction after propofol was

significantly greater than after thiopentone in both the infants and older children (P = 0.011). The magnitude of arterial pressure reduction after propofol was similar to that found in other paediatric studies [Morton *et al*, 1988; Hannallah *et al*, 1991] and to the earlier haemodynamic study in this thesis (page 68).

In healthy adults, thiopentone produces a reduction in arterial pressure and cardiac output, with or without a compensatory increase in total systemic vascular resistance [Elder *et al*, 1955; Etsten and Li, 1955; Flickinger *et al*, 1961] and a decrease in baroreflex sensitivity, associated with tachycardia [Bristow *et al*, 1969]. The cardiovascular depression caused by thiopentone is due to a combination of depression of the vasomotor centre [Skovsted, Price and Price, 1970] and direct myocardial depression [Conway and Ellis, 1969; Sonntag *et al*, 1975]. Venodilatation, causing a sequestration of blood volume in the venous side of the circulation, and, a reduction in the left ventricular diastolic filling and stroke volume, have also been suggested [Eckstein, Hamilton and McCammond, 1961]. The effect on arterial resistance vessels is variable as demonstrated by the inconsistent changes in systemic vascular resistance with barbiturates.

The children receiving thiopentone in this study had a significant reduction in arterial pressure and cardiac index. However systemic vascular resistance decreased rather than increased. The changes in heart rate were different between the two age groups. The mean heart rate increased in the older children but decreased in the infants (Figure 5. 1), suggesting that the compensatory mechanisms are less efficient in infants. A comparative study of thiopentone in infants and children, observed a greater degree of myocardial depression than that in the present study [Tibballs and Malbezin, 1988b]. This was probably related to the larger dose of thiopentone (7.5 to 8.5 $mg.kg^{-1}$) and concomitant use of

suxamethonium in that study.

Studies of the mechanism of propofol induced hypotension in adults have produced conflicting results [Fairfield, Dritsas and Beale, 1991; Lippmann *et al*, 1991]. Lippmann and coworkers [1988] observed a reduction in left ventricle stroke work index (35%) and cardiac index (18%) with no significant decrease in systemic vascular resistance and pulmonary vascular resistance. Andreev *et al* [1988] using seven patients with Jarvik -7 artificial heart to control the variation in preload and cardiac output, showed that the cardiovascular depression was due to a peripheral vasodilatation involving venous, pulmonary and arterial vessels. Gauss *et al* [1991] using echocardiographic assessment and end-systolic quotient as an indicator of inotropy found that propofol-induced hypotension as a result of simultaneous negative inotropy and reduction in afterload. Grounds *et al* [1985] observed a significant decrease in total systemic vascular resistance (18%) with minimal changes in heart rate and cardiac output. Fairfield, Dritsas, and Beale [1991] suggested that propofol has a biphasic effect on the cardiovascular system. After injection, there was a marked reduction in SVR with a compensatory tachycardia and increased cardiac output and the arterial pressure decreased despite the compensatory effects. This was followed by an increased in SVR towards baseline, a decrease in heart rate and cardiac output with a further reduction in arterial pressure.

The magnitude of hypotension after propofol in this study, was similar to that in adults [Grounds *et al*, 1985]. It was associated with a significant reduction in both cardiac index (10 - 15%) and systemic vascular resistance (15 - 19%). Heart rate in the older children did not change, but it decreased significantly in the infants. The decrease was statistically but not clinically significant (Figure 5. 1). No biphasic effect, as described by Fairfield and colleagues [1991] was observed in the

children who received propofol in this study. More infants were crying on arrival in the operating theatre than the older children and this may have caused an increase in sympathetic tone resulting in a higher heart rates and systemic vascular resistance. Anaesthesia attenuates sympathetic tone and this may have contributed to the greater reduction in heart rate in the infants. However heart rates were all within the physiological range (Figure 5.1). Baroreceptor reflexes have been found to be more attenuated in both young animals and humans anaesthetized with halothane [Wear, Robinson, and Gregory, 1982; Gregory, 1982] or nitrous oxide [Duncan, Gregory, and Wade, 1981] when compared with adults. The difference in the reduction of heart rate is probably a reflection of a more significant baroreceptor impairment in the infants than in the older children. The decrease in heart rate after propofol was greater than after thiopentone. This suggests that propofol causes more baroreflex depression than thiopentone, similar to previous studies in adult patients [Cullen *et al*, 1987; Ebert *et al*, 1992]. Propofol has been shown to cause a prolongation of the QT interval and results in a higher incidence of bradycardia and junctional rhythm than thiopentone or methohexitone in children [Saarnivaara, Hiller and Oikkonen, 1993]

Paediatric patients are thought to have a limited ability to increase myocardial contractility and heart rate is an important factor in determining the cardiac output [Robinson, 1983]. However the infants in this study showed an increase rather than a decrease in stroke volume index associated with the reduction in heart rate. This suggests that the myocardium is capable of increasing stroke volume in this age group. Ventricular diastolic filling time and stroke volume are inversely proportional to baroreceptor reflex-mediated changes in heart rate. The net effect of these haemodynamic responses produced a nonsignificant difference in the reduction of cardiac index in all four groups. Like

thiopentone, there was no compensatory rise in systemic vascular resistance following propofol.

Haemodynamic effects during anaesthesia are affected by perioperative factors including drugs administered concurrently. Diazepam premedication was necessary to reduce anxiety and allow baseline haemodynamic measurements. A dose of 0.4 $mg.kg^{-1}$ was used because at lower doses, excitement may occur from a lack of inhibition [Kosarussavadi, 1991]. Its use as premedication is not associated with significant cardiovascular depression [Fell *et al*, 1985]. Any incidental haemodynamic effects caused by the premedication should be considered as relevant to the use of these induction agents in the clinical setting.

Halothane and nitrous oxide have been shown to impair baroreflexes by resetting the baroreceptors [Bristow *et al*, 1969]. Nitrous oxide preserves the sympathetic reflex to the vascular smooth muscle in skeletal muscle [Ebert, 1990], and may counteract the negative cardiovascular effects of the other agents during induction. Concurrent use of these two inhalational agents may be criticized, but it reflects the situation observed in common clinical practice.

In conclusion, propofol, as an induction agent, produces more hypotension than thiopentone. However there was no significant difference in the reduction of cardiac index between the two agents, and the degree of haemodynamic changes was acceptable in healthy children with either agents.

Based on the two haemodynamic studies, it is suggested that, although the degree of hypotension after propofol is not of clinical significance in most instances, one should avoid propofol or modify the induction technique in patients with compromised circulatory function. A slower rate of administration of propofol or pretreatment with a vagolytic agent may be used.

CHAPTER 6

Single Dose Pharmacokinetics

SINGLE DOSE PHARMACOKINETICS

Introduction

Studies have consistently shown that children require a larger dose of propofol for induction of anaesthesia than adults [Purcell-Jones *et al*, 1987; Morton *et al*, 1988; Mirakhur, 1988; Valtonen *et al*, 1988; Patel *et al*, 1988; Hannallah *et al*; 1991; Manschot *et al*, 1992]. Similarly, in infusion studies, children were found to require a higher infusion dose than adults for maintenance of anaesthesia [Browne, Wolf, and Prys-Roberts, 1990; Browne, Prys-Roberts and Wolf 1990, 1992; Marsh *et al*, 1991].

Age-related physiological changes in the distribution of body water, and cardiovascular, hepatic, and renal function may affect the distribution, metabolism, and excretion of drugs. Special anaesthetic problems occur mostly in children under three years old [Annotation, 1978; Hatch, 1984] and in terms of pharmacokinetics, they represent a separate sub-group [Hull, 1991]. It is, therefore, possible that the increased requirement of propofol in younger children when compared with older children ["Induction dose requirement" study page 52; Morton *et al*, 1988; Westrin, 1991], may, in part, be due to differences in the disposition of propofol. To test this hypothesis, disposition after a single intravenous dose of propofol was studied in children between one to twelve years old. The protein binding of propofol in children was also compared with that of adults. Propofol kinetics in children so far have only been studied in children older than three years old in the English language literature [Saint-Maurice *et al*, 1989; Valtonen *et al*, 1989a; Jones, Chan, and Andrew, 1990].

Methods

Pharmacokinetic study

The study was performed on 26 healthy children aged between one and 12 years old undergoing elective minor surgery. Those who were grossly obese; who had a haemoglobin level less than 11.5 $g.dl^{-1}$, systemic disease, a history of allergy or an adverse reaction to previous anaesthetics were excluded from the study.

No premedication was given except for the application of EMLA cream to the dorsum of both hands about an hour before anaesthesia. Anaesthesia was induced with propofol 2.5 $mg.kg^{-1}$ administered over a 20-s period and the tracheal was intubated after atracurium 0.5 $mg.kg^{-1}$. Ten milligram of lignocaine 2% was added to every 200 mg of propofol just before administration. Anaesthesia was maintained with 70% nitrous oxide and 0.5% halothane in oxygen. The patients' lungs were ventilated mechanically to maintain an end-tidal CO_2 concentration between 4.6 and 5.3 kPa. Analgesia was provided by an appropriate regional block using bupivacaine. Intravenous fluid 0.18% saline in 4.3% dextrose was given at the maintenance rate until the patient could take oral fluids postoperatively. At the end of anaesthesia, residual neuromuscular block was antagonised with neostigmine and atropine.

Venous blood samples (1.5 ml) were taken before induction of anaesthesia and at 2, 4, 6, 10, 15, 30, 45, 60, 120, 240, 360, 480, 720 minutes following propofol administration. The baseline sample was obtained from the intravenous cannula used for administration of propofol. A second cannula was placed on the opposite arm after the patient was asleep. Exact time of sampling was noted for those samples which were taken outside the protocol time.

Protein Binding study

Plasma protein binding of propofol was studied in a different 22 healthy children between 1-12 years old and compared with 11 healthy adults between 20-40 years old. A nine millilitre venous blood sample was obtained before anaesthesia for protein binding study, albumin and α_1 acid glycoprotein assays. The reason for studying separate patients was to limit the volume of blood obtained for sampling from each individual patient.

Handling of all the blood samples and subsequent analysis were as described in Chapter 2 (page 38). The pharmacokinetic parameters were estimated by a two-stage approach, using both model independent and compartmental methods. In the compartmental analysis, individual concentration versus time plots were fitted to a tri-exponential equation as this function was found to fit best in previous pharmacokinetic studies [Saint-Maurice *et al*, 1989; Valtonen *et al*, 1989a; Jones, Chan, and Andrew, 1990; Kataria *et al*, 1994].

Statistical Analysis

The pharmacokinetic values obtained were correlated with body weight, and age after being standardized for body weight using the program incorporated in the MKMODEL program. Kruskal-Wallis or Mann Whitney U-test were used to compare the protein binding data.

Results

Data from three patients were excluded from the analysis because the blood sampling was incomplete. The demographic data of the twenty-three children selected for the analysis are provided in Table 6. 1.

TABLE 6.1. *Patients demographic data*

No.	Name	Age (yr)	Sex	Body wt (kg)	Surgery
1	LWY	1.0	M	13.4	Orchidopexy
2	YTH	1.2	M	10.9	Herniotomy
3	TYH	1.5	M	12.0	Orchidopexy
4	LCF	1.6	M	13.2	Orchidopexy
5	WKP	1.66	M	13.2	Herniotomy
6	TPW	2.0	M	12.0	Orchidopexy
7	CCW	1.7	M	11.7	Ex. branchial sinus
8	TCY	2.0	M	12.5	Herniotomy
9	CCH	2.2	M	12.5	Herniotomy
10	AYYF	2.25	M	12.2	Herniotomy
11	LCL	3.0	M	10.7	Orchidopexy
12	YKN	4.5	M	17.5	Ex. chest wall sinus
13	NSK	4.7	M	15.4	Circumcision
14	CKS	4.8	M	18.5	Herniotomy
15	LHL	5.33	M	17.0	Circumcision
16	LKS	5.5	M	17.7	Herniotomy
17	YKW	6.5	M	17.3	Circumcision
18	TYH	7.0	M	22.4	Circumcision
19	LHI	8.0	M	25.8	Circumcision
20	TFL	10.0	M	24.7	Orchidopexy
21	WKH	10.0	M	35.0	Repair buried penis
22	NQD	12.0	M	30.0	Circumcision
23	YHM	12.0	M	31.5	Ligation testicular vein

The individual blood concentration versus time profile of all patients is displayed in Figure 6.1.

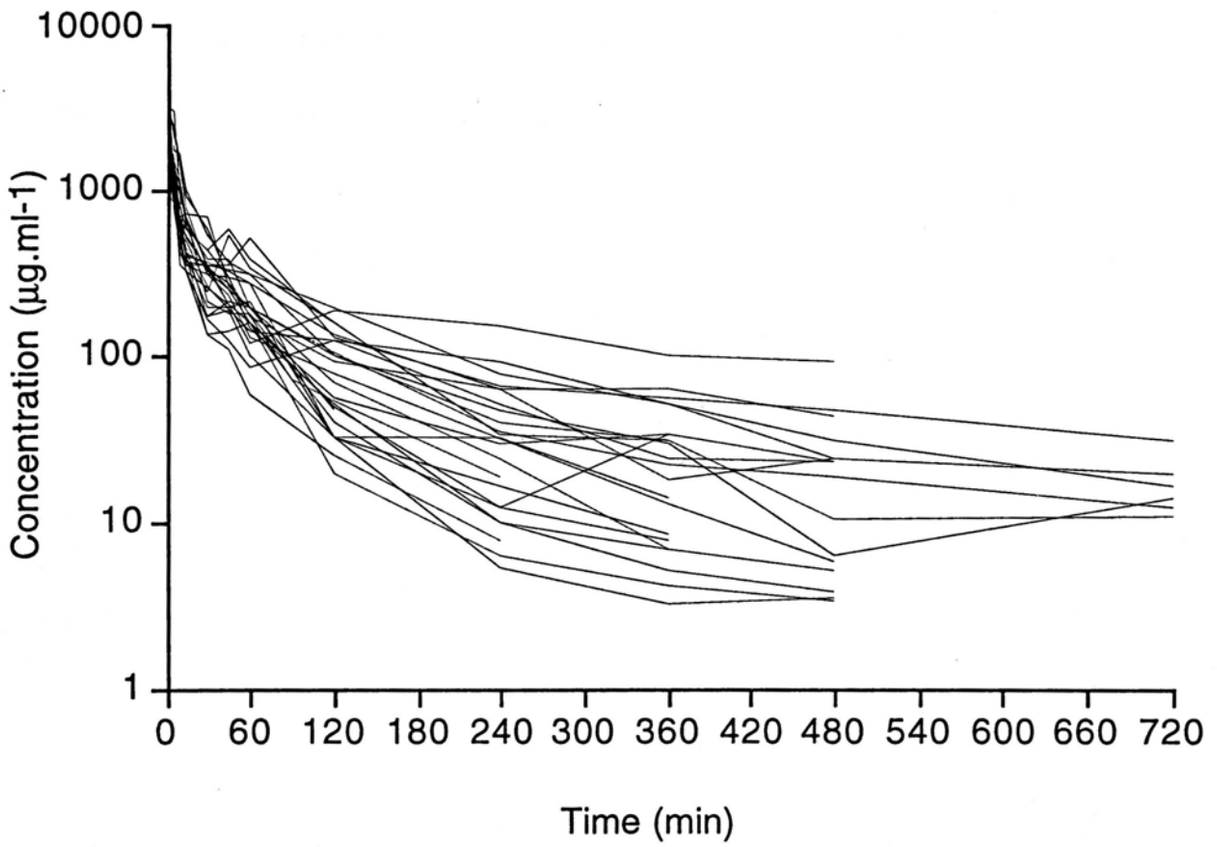


FIGURE 6.1. The individual blood concentration time profile for all 23 children. Blood samples with non detectable propofol concentration were not plotted on the graph. Sixteen patients had detectable propofol concentration at 480 minute time and only six patients at 720 minute time.

The individual blood concentrations are listed in Appendix C (page 210). The blood propofol concentrations decreased with time in all patients, but secondary peaks or plateauing of the concentrations were observed in nine patients between 45 and 120 minutes after the administration of propofol. At eight hours after propofol, only 16 patients had detectable propofol concentrations and the number decreased to only six by 12 hours' time (Figure 6. 1).

The individual and mean (SD) pharmacokinetic variables obtained from the model independent and compartmental analysis are listed in Tables 6. 2 and 6. 3. The mean apparent volume of distribution at steady state (V_{SS}) and clearance (Cl) derived from the two methods of pharmacokinetic analysis were very similar. During the estimation of the pharmacokinetic variables, the area under the extrapolated part of the concentration-time plot was 1.82% (range 0.19% to 7.23%) of the total area under the curve.

Correlation regression analysis of weight and the V_{SS}(NC) and Cl(NC), V_C(C) and Cl(C) revealed a good correlation. The r values were 0.754, 0.817, 0.781 and 0.798, respectively. All the p values were < 0.001. However, there was no correlation between age and any of the pharmacokinetic variables after being standardized for weight [V_{SS}(NC) ($r = 0.216$, $p = 0.33$), Cl(NC) ($r = 0.245$, $p = 0.25$), MRT ($r = 0.04$, $p = 0.852$), V_C(C) ($r = 0.025$, $p = 0.92$) and Cl (C) ($r = 0.231$, $p = 0.288$)]. The hybrid rate constants and derived micro rate constants from the compartmental analysis are listed in Table 6.4.

TABLE 6.2. *Pharmacokinetic data from the noncompartmental analysis*

No.	Patients	$V_{ss(NC)}$ l. kg^{-1}	Cl(NC) $ml.min.^{-1}kg^{-1}$	MRT min	AUC $\mu g,min.^{-1}ml^{-1}$
1	LWY	4.23	56.69	74.61	44.10
2	YTH	3.13	41.26	75.97	62.26
3	TYH	2.16	54.10	39.84	46.21
4	LCF	3.08	28.16	109.31	88.78
5	WKP	4.90	25.42	192.29	98.35
6	TPW	2.14	24.84	86.07	100.64
7	CCW	4.25	33.01	128.80	77.67
8	TCY	2.70	56.46	47.81	43.92
9	CCH	5.61	84.21	66.67	29.69
10	AYYF	1.52	40.66	37.46	61.48
11	LCL	9.20	38.62	238.17	65.33
12	YKN	4.86	57.04	85.26	44.08
13	NSK	5.29	27.53	192.20	90.81
14	CKS	3.34	91.17	36.67	27.27
15	LHL	3.66	47.51	77.09	52.62
16	LKS	5.33	37.78	141.16	66.54
17	YKW	6.59	87.35	75.49	28.45
18	TYH	6.84	78.30	87.32	31.93
19	LHI	5.82	46.71	124.63	53.94
20	TFL	4.55	58.63	77.63	42.81
21	WKH	3.57	64.66	55.24	38.89
22	NQD	5.52	37.46	147.44	66.74
23	YHM	2.94	55.96	52.46	44.53
Mean		4.40	51.02	97.81	56.83
SD		1.78	19.82	54.16	22.26

TABLE 6.3. *Pharmacokinetic data from compartmental analysis*

No.	Patient	V_c (C) $l.kg^{-1}$	V_{ss}(C) $l.kg^{-1}$	Cl(C) $ml.min^{-1}.kg^{-1}$	$t_{1/2\alpha}$ min	$t_{1/2\beta}$ min	$t_{1/2\gamma}$ min
1	LWY	0.69	5.06	54.25	2.40	22.91	171.11
2	YTH	0.57	2.84	40.20	1.31	13.55	103.51
3	TYH	0.73	1.96	55.32	3.45	30.74	676.12
4	LCF	0.51	2.96	28.55	3.42	20.49	182.24
5	WKP	0.37	3.82	24.30	4.11	6.10	144.34
6	TPW	0.42	4.08	24.84	4.74	49.28	355.40
7	CCW	0.68	6.14	30.67	2.39	50.44	465.67
8	TCY	0.81	2.40	55.48	5.43	18.29	50.85
9	CCH	1.22	4.99	80.76	4.07	21.35	63.38
10	AYYF	0.42	1.37	40.93	3.68	16.07	52.23
11	LCL	0.46	8.96	38.01	1.49	4.09	216.98
12	YKN	0.75	3.88	58.31	3.34	51.75	162.03
13	NSK	0.62	6.47	23.84	2.04	5.75	215.07
14	CKS	0.88	2.87	89.99	4.03	42.33	43.44
15	LHL	0.42	2.98	45.90	1.11	7.82	82.23
16	LKS	0.92	8.59	35.32	3.98	37.70	432.74
17	YKW	1.03	5.04	87.22	2.94	31.45	205.70
18	TYH	0.73	4.02	78.08	2.23	28.25	163.01
19	LHI	0.36	5.41	43.40	1.16	10.43	132.88
20	TFL	0.47	2.98	57.37	1.76	03.44	56.52
21	WKH	0.86	6.98	71.08	1.52	33.37	319.54
22	NQD	0.67	7.52	34.41	1.61	16.15	226.31
23	YHM	0.56	2.67	50.98	2.02	46.94	457.82
Mean		0.66	4.50	49.96	2.79	24.72	216.48
SD		0.23	2.10	20.24	1.24	15.89	164.30

TABLE 6.4. *Hybrid rate constants and derived microrate constants of individual patients.*

No.	Name	α (min^{-1})	β (min^{-1})	γ (min^{-1})	k10 (min^{-1})	k12 (min^{-1})	k13 (min^{-1})	K21 (min^{-1})	k31 (min^{-1})
1	LWY	0.2883	0.0302	0.0041	0.0792	0.1320	0.0265	0.0792	0.0056
2	YTH	0.5284	0.0511	0.0067	0.0710	0.2280	0.0322	0.2447	0.0104
3	TYH	0.2006	0.0225	0.0010	0.0760	0.0876	0.0002	0.0593	0.0010
4	LCF	0.2026	0.0338	0.0038	0.0564	0.0724	0.0219	0.0840	0.0055
5	WKP	0.1686	0.1135	0.0048	0.0653	-0.0665	0.1956	0.0732	0.0192
6	TPW	0.1462	0.0141	0.0020	0.0595	0.0571	0.0169	0.0262	0.0026
7	CCW	0.2903	0.0137	0.0015	0.0451	0.1780	0.0103	0.0702	0.0019
8	TCY	0.1276	0.0379	0.0136	0.0683	0.1921	-0.1434	0.0300	0.0322
9	CCH	0.1701	0.0325	0.0109	0.0660	0.0798	0.0070	0.0278	0.0328
10	AYYF	0.1884	0.0431	0.0133	0.0985	0.0383	0.0310	0.0581	0.0188
11	LCL	0.4636	0.1694	0.0032	0.0823	0.0709	0.2228	0.2479	0.0123
12	YKN	0.2076	0.0134	0.0043	0.0782	0.1049	0.0047	0.0329	0.0046
13	NSK	0.3389	0.1205	0.0032	0.0384	0.0419	0.2105	0.1488	0.0230
14	CKS	0.1720	0.0164	0.0160	0.1025	0.0595	-0.0005	0.0259	0.0169
15	LHL	0.6227	0.0886	0.0084	0.1092	0.2447	0.0826	0.2672	0.0159
16	LKS	0.1741	0.0184	0.0016	0.0384	0.0804	0.0163	0.0566	0.0024
17	YKW	0.2355	0.0220	0.0034	0.0848	0.1095	0.0072	0.0559	0.0037
18	TYH	0.3108	0.0245	0.0043	0.1063	0.1540	0.0098	0.0648	0.0047
19	LHI	0.5974	0.0664	0.0052	0.1199	0.2461	0.1584	0.1316	0.0131
20	TFL	0.3938	0.2017	0.0123	0.1212	0.0335	0.1542	0.2691	0.0299
21	WKH	0.4556	0.0208	0.0022	0.0831	0.2827	0.0107	0.0995	0.0025
22	NQD	0.4305	0.0429	0.0031	0.0512	0.2089	0.0687	0.1398	0.0079
23	YHM	0.3426	0.0148	0.0015	0.0912	0.2107	0.0000	0.0555	0.0015
mean		0.3068	0.0527	0.0057	0.0779	0.1237	0.0497	0.1021	0.0117
SD		0.1490	0.0520	0.0045	0.0241	0.0872	0.0854	0.0805	0.0102

The data on protein binding are displayed in Table 6.5. The mean plasma albumin concentration in children one to three years old was significantly higher than those in the older children and adults ($p < 0.05$). However, there was no difference when the values from the two groups of children were compared. The total protein and α_1 acid glycoprotein concentrations were similar in the three age-groups. The mean propofol free fraction was lowest in the one to three years old children, highest in the adults and intermediate in the children between four and 12 years old. However, the differences did not reach statistically significant level and there was no correlation between the albumin concentrations and the free propofol fractions ($r = 0.127$)

TABLE 6.5. *Protein binding data , Mean (SD)*

	Age (yr)	body wt (kg)	Pl protein binding (%)	Free propofol (%)	Total protein $g.l^{-1}$	Albumin $g.l^{-1}$	$\alpha_1$acid glycoprotein $mg.l^{-1}$
Children <3 yr (n= 12)	2.1 (0.8)	12.8 (1.9)	98.8 (0.3)	1.2 (0.3)	70.3 (7.4)	47.3(2.3)	535.8 (146.0)
Children 3-12 yr (n=10)	8.6 (3.6)	29.6 (12.3)	98.6 (0.4)	1.4 (0.4)	71.9 (5.5)	45.2 (2.8)	514.0 (115.3)
Adults (n= 11)	29.6 (4.8)	70.0 (9.9)	98.4 (0.4)	1.6 (0.4)	75.1 (4.0)	44.6 (2.5)	665.45 (27.7)
p value			0.1317	0.1317	0.15	0.047	0.24

Discussion

The pharmacokinetic parameters from previous single dose studies in children [Saint-Maurice *et al*, 1989; Valtonen *et al*, 1989a; Jones, Chan, and Andrew, 1990] (Table 6.6) vary somewhat with each other. The reasons include differences in the methodologies, small population samples, the limited accuracy in single-dose kinetic studies and possibly the difference in ethnic origins of the patients [Morton *et al*, 1992].

TABLE 6. 6. Pharmacokinetic data from other paediatric single bolus dose studies

	Saint - Maurice et al (1989)	Valtonen et al (1989)	Jones et al (1990)	Kataria et al (1992)
Age range (yr)	4-7	3-10	4-12	3-11
no. of patient	10	8	12	21
	mean (SEM)	Mean (SD)	Mean (SEM)	Mean (SEM)
Vc ($l.kg^{-1}$)	0.722 (0.11)	0.530 (0.65)	0.597 (0.10)	0.78 (0.07)
Vss ($l.kg^{-1}$)	10.90 (1.20)	2.16 (1.49)	5.01 (2.66)	
Cl ($ml.min.^{-1} kg^{-1}$)	30.6 (2.9)	32.0 (16.8)	40.4 (3.6)	57.0 (2.0)
t1/2α (min)	4.15 (0.78)	1.50 (1.56)	3.05 (0.43)	3.8 (0.39)
t1/2β (min)	56.1 (6.30)	9.3 (3.78)	24.3 (5.13)	51.5 (6.9)
t1/2γ (min)	735.0 (82.7)	214.6 (168.8)	209.22 (29.3)	

Saint-Maurice and colleagues [1989] observed a 70% increase in the central volume of distribution in children compared with young adults

with a similar clearance value. Valtonen and colleagues [1989a] highlighted a shorter $t_{1/2\beta}$. Jones and co-workers [1990] in their study of Chinese children had similarly observed a shorter $t_{1/2\beta}$ and $t_{1/2\gamma}$ (50% and 33% of the adults' values respectively). However, in spite of the variations, some general features are observed in children. The mean central compartment volume is larger, and the clearance value is higher than in adults.

In this study, although there was a significant correlation of the pharmacokinetic parameters with body weight, there was no correlation of age with any of the pharmacokinetic variables after being standardized for body weight. This is consistent with the findings by Kataria and associates in paediatric patients [1992; 1994]. This result suggests that the difference in the dose requirements between the different age groups of children (above one year) is unlikely to be due to the age-related differences in pharmacokinetics. However pharmacodynamic differences cannot be ruled out. The central nervous system may have a different sensitivity to anaesthetic agents at different ages. Examination of phenobarbitone concentrations in neonatal brain tissue at autopsy had shown that the brain/plasma concentration ratio increases with gestational age [Painter *et al*, 1981]. Furthermore, Onishihi and colleagues [1984] reported lower brain/serum phenobarbitone ratios in children than in adults. These data suggest that a higher serum phenobarbitone concentration is required in the younger age groups for comparable efficacy [Gilman, 1990]. Marsh and colleagues [1991] using a computer controlled propofol infusion system, have observed that children needed a higher target-concentration than adults to achieve a satisfactory induction. Similarly, thiopentone pharmacokinetics in children were not significantly different from those in adults [Sorbo, Hudson, and Loomis, 1984], although children 5-15 years required more thiopentone than adult patients [Coté *et al*, 1981].

This study may be criticized for the use of venous blood samples, inadequate early sampling after induction, and a short duration of blood sampling in the postoperative period. Propofol has a significant uptake into tissues, leading to the initial venous concentration being substantially lower than the arterial blood concentration. Ideally, arterial blood sampling should be used for a pharmacokinetic study. However strong ethical considerations prevented frequent sampling and using arterial blood to gain the maximal pharmacokinetic information.

The high incidence of secondary peaks in children may reduce the confidence in variables calculated by compartmental analysis because peaks affect the accuracy of curve fitting [Gin *et al*, 1990]. These peaks have been attributed to patient movements causing redistribution of propofol [Kay *et al*, 1986; Cockshott *et al*, 1987a; Gepts and Camu, 1991]. In the current study, two methods (model independent and compartmental) of pharmacokinetic analysis were used for comparison. Population derived pharmacokinetics may be unreliable because of the large interpatient differences in children [Kearns and Reed, 1989; Gilman, 1990]. The mean volume of distribution at steady state (V_{SS}) and clearance (Cl) values obtained by the two methods were almost identical (Table 6.2 and 6.3) and overall, the methodology appears valid. Kataria and coleagues [1994] in their thorough evaluation of the three approaches in the determination of propofol pharmacokinetics in children, found that the two stage, naive pooled technique and the mixed effects population analysis, which included the patient covariates in the estimation, gave similar results. The weight adjusted model provided a significant better description of the pharmacokinetic data but not the age factor.

The results of bolus kinetic studies are often very variable in children and therefore difficult to compare. Studies vary in their methodology and pharmacokinetic analysis. Technically, multiple blood samples are

difficult to obtain and venous blood samples are usually used for pharmacokinetic analysis which are less accurate than arterial samples; in addition, accurate timing of blood samples is difficult. Furthermore there is a significant interindividual variation among the paediatric population. Polyexponential pharmacokinetics are not easily interpreted by simple examination and comparison of pharmacokinetic variables [Shafer, 1993]. However, a comparison with two paediatric and two adult studies was attempted after estimation of the confidence intervals of various pharmacokinetic parameters. The values are listed in Table 6.7. The study by Jones and associates was chosen because their patients are of a similar ethnic origin as this study, and that of Kataria and associates was selected because of their large series of data. The adult studies by Kirkpatrick and colleagues [1988] and Gin and associates [1990] were chosen because their methodology is comparable to the current study. Their patients were mechanically ventilated, single dose propofol was given, venous samples were used, and the timing of sampling was similar.

TABLE 6. 7. *Comparison of propofol pharmacokinetic parameters estimated in the current study with other paediatric and adult studies 95% confidence intervals (estimated from the original values of mean and SD or SEM or % CV) in square brackets.*

	Current study (bolus)	Jones et al (1990) (bolus)	Kataria et al (1992) (bolus)	Kataria et al (1994) (mixed)*	Infusion study (chapter 7)	Kirkpatrick et al (1988) (bolus)	Gin et al (1990) (bolus)
Age range (yr)	1-12	4-12	3-11	3-11	4-10	18-35	33.3 (SD 2.7)
no. of patient	23	12	21	56	10	12	6
values presented	mean (SD) [95% CI]	mean (SEM) [95% CI]	mean (SEM)	mean (% CV) [95% CI]		mean (SEM) [95% CI]	mean (SD) [95% CI]
Vc ($l.kg^{-1}$)	0.66 (0.22)	0.597 (0.10)	0.78 (0.07)	0.32 (103%)	0.432	0.42 (0.055)	0.48 (0.15)
	[0.56 to 0.75]	[0.38 to 0.82]	[0.63 to 0.93]	[0.23 to 0.41]		[0.29 to 0.54]	[0.38 to 0.55]
Vss ($l.kg^{-1}$)	4.40(1.78)	5.01 (2.66)		7.2		11.9 (3.5)	3.54 (1.83)
	[3.63 to 5.17]	[- 0.84 to 10.86]				[4.2 to 19.6]	[2.79 to 5.46]
Cl	49.96 (20.24)	40.4 (3.6)	57.0 (2)	37 (40%)	41.7	27.7 (2.3)	28.76 (5.93)
($ml.min.^{-1} kg^{-1}$)	[41.19 to 58.67]	[32.48 to 48.32]	[52.83 to 61.17]	[33.04 to 40.96]		[22.64 to 32.76]	[22.54 to 34.98]
t1/2α (min)	2.79 (1.24)	3.05 (0.43)	3.8 (0.39)	2.0		2.04 (0.27)	
t1/2β (min)	24.72 (15.89)	24.3 (5.13)	51.5 (6.9)	27.0		52.4 (9.2)	21.6 (10.0)
t1/2γ (min)	216.48 (164.3)	209.22 (29.3)		329		674 (122)	

* Two stage approach analysis.

Considering the differences in methodology, the pharmacokinetic variables from this study are quite similar to the single bolus kinetic studies by Jones and associates [1990] and by Kataria and co-workers in 1992, but different from those in the mixed population data (bolus and infusion method of administration) in the more recent paper by Kataria and co-workers in 1994, and the infusion modelling kinetic study in this thesis (Chapter 7, page 111). The central volume of distribution estimated from the current bolus study is larger and clearance is higher than the corresponding values in the infusion method. Similar difference is observed in the pharmacokinetic parameters in the two reports by Kataria and colleagues [1992; 1994] (Table 6.7). These findings confirm that single dose kinetic parameters are poor predictors for infusion administration. Most of the bolus studies had inadequate early and late blood samples. An adult kinetic study has similar finding [Schüttler, Stoeckel and Scwilden, 1985]. There was a significant correlation between the sampling period, volume of distribution and terminal half-life, and an inverse relationship between the sampling period and clearance [Campbell *et al*, 1988]. According to them, a sampling period of 52 hours is still inadequate to define the terminal elimination phase. Therefore the clearance values are generally overestimated and the terminal half-lives and volume of distribution are underestimated in most studies.

A larger central volume of distribution and higher clearance in children than the values from adult studies [Kirkpatrick *et al*, 1988; Gin *et al*, 1990] may partly explain why children require a larger induction dose of propofol than adults. The higher mean ratio of k_{31}: k_{10} obtained in the current study compared with that in the study by Kirkpatrick and colleagues (0.1489 vs 0.0247) suggests that propofol returns faster from the peripheral compartment back to the central compartment for elimination. An increase in the clearance of many intravenous drugs

during childhood have been observed [Morselli, Franco-Morselli and Bossi, 1980; Sorbo, Hudson, and Loomis, 1984, Roure *et al*, 1987; Olkkola, Maunuksela, and Korpela, 1989].

In summary, there is no age-related differences in the pharmacokinetics parameters in this study to explain the difference in dose requirements in different age groups of children. The clinical application is that theoretically, during an infusion study, one single algorithm should be applicable for children from age one to 12 years. In other words, it is not necessary to use different pharmacokinetic parameters for different age groups of children. However, the target concentration required may be different from that suggested by the differences in pharmacodynamic response. The decision on dosage of propofol in paediatrics should take both pharmacokinetics and pharmacodynamic titration into consideration.

SECTION IV
MAINTENANCE OF ANAESTHESIA

CHAPTER 7

Pharmacokinetic-Model-Controlled Infusion of Propofol

PHARMACOKINETIC MODEL CONTROLLED INFUSION OF PROFOFOL

Introduction

Drugs for intravenous induction of anaesthesia have often been tried as a sole anaesthetic. Early experiences were frequently disastrous as the pharmacokinetics and toxicity of these drugs were not truly understood [Savege, 1979]. The interest in total intravenous anaesthesia in adults as well as in children has been rekindled by the availability of drugs such as propofol and alfentanil which have suitable pharmacokinetic and pharmacodynamic profiles.

Earlier infusion regimens for propofol have been a mixture of bolus and linear infusion techniques [Roberts *et al*, 1988; Shafer *et al*, 1988; Browne, Wolf, and Prys-Roberts, 1990; Browne, Prys-Roberts and Wolf, 1992]. However, this method has limited accuracy and flexibility and there is also, a need to remember the formulae for the infusion schedules.

Infusion of intravenous agents for maintenance of anaesthesia has been simplified by the availability of computer-controllable infusion pumps that can be programmed to maintain a constant theoretical plasma concentration using appropriate pharmacokinetic algorithms [White and Kenny, 1990]. However, successful use of these algorithms requires a knowledge of plasma concentration-effect relationships for the drug in use and of the accuracy of the algorithm.

In this study, the use of an algorithm for administering propofol to paediatric patients [Marsh *et al*, 1991] to maintain anaesthesia was tested prospectively in Chinese children between four and 10 years old. The quality of anaesthesia using a propofol infusion delivered by this system

will be examined in conjunction with the recovery characteristics in the Chapter 8 (page 131).

Methods

The infusion system, controlling algorithm and rate constants for a three-compartment open model used to control the infusion rates are described in the method chapter (page 45).

Thirty healthy children (ASA I) aged between four and 10 were studied. They had been full term babies, had no contraindications to the drugs used in the trial, had a haemoglobin level of more than 11.5 $g.dl^{-1}$ and were undergoing minor surgical procedures associated with minimal blood loss. EMLA cream was applied to the dorsum of one hand, one hour preoperatively to assist with intravenous catheter placement. Anaesthesia was induced with intravenous propofol given by an infusion pump and maintained using the propofol infusion and nitrous oxide 70% in oxygen. All patients breathed spontaneously. A Rees modification of Ayre's T piece and laryngeal mask airway were used for children who weighed less than 20 kg. A Magill system was used instead for those who were over 20 kg.

The study was conducted in two parts. In the first part, ten patients were studied to determine the accuracy of the paediatric infusion algorithm by Marsh and colleagues [1991] in the local paediatric population. For the first patient, the initial target plasma concentration of propofol was set at 10 $\mu g.ml^{-1}$. This initial plasma concentration was then adjusted up or down by 2 $\mu g.ml^{-1}$ for each subsequent patient according to whether or not the previous patient moved in response to surgical incision, which was made between five and 10 minutes after anaesthetic induction. Post-operative analgesia was provided at the end of the

procedure using bupivacaine 0.25% (maximum 2.0 $mg.kg^{-1}$) by either direct infiltration into the operation site by the surgeon or local nerve block performed by the anaesthetist. The target concentration of propofol was adjusted to maintain a satisfactory depth of anaesthesia according to standard clinical criteria, including no movement in response to surgical stimuli and maintaining arterial pressure and heart rate within 20% of baseline values. Arterial oxygen saturation, noninvasive arterial pressure, heart rate and end tidal carbon dioxide were monitored throughout the procedure. Time from switching off the infusion until eye opening in response to verbal command was recorded.

After analysis of the results of the first part of the study, the accuracy of the pharmacokinetic algorithm was improved using linear least squares regression. Another 20 patients were then studied prospectively to test the accuracy of the revised pharmacokinetic model. These patients were also part of a subsequent comparative study of the anaesthesia and recovery characteristics of paediatric patients undergoing minor elective surgery, using four anaesthetic techniques (Chapter 8, page 132). The anaesthetic technique was identical to that used in the first part of the study except that the initial plasma concentration was 8 $\mu g.ml^{-1}$, rectal paracetamol 10-20 $mg.kg^{-1}$ was administered and the local anaesthetic block was placed before commencing surgery. The initial blood concentration of 8 $\mu g.ml^{-1}$ was equivalent to a bolus dose of 3.5 $mg.kg^{-1}$ propofol.

A second intravenous catheter was placed in a large vein in the opposite limb to that used for the propofol infusion after the patient was asleep. It was used for taking venous blood samples for later analysis of blood propofol concentrations. Two millilitre blood samples were drawn at the time of surgical incision and then at 5 - 10 minute intervals throughout the procedure. Up to five samples were also taken in the

recovery room during the first two hours following termination of the infusion. A maximum of twelve blood samples were obtained from each patient. Handling of blood samples and subsequent analysis are described in Chapter 2 (page 38).

Statistical analysis

Blood concentrations of propofol were compared with the concentrations predicted by the pharmacokinetic algorithm to calculate prediction error, bias and precision of the algorithm (Chapter 2, page 49). This was calculated for each patient and the overall mean values estimated. For patients in the second part of the study, precision during the infusion phase was also calculated for each individual about that individual's bias during infusion phase to test the ability of the infusion model to maintain a constant plasma concentration. This procedure was not performed for patients in the first part of the study because of the small number of patients studied and the small number of blood samples obtained. An iterative linear least-squares regression program which minimized the total squared prediction error for each patient, was performed to find revised rate constants that would best fit the study population. The mean squared errors for each patient before and after least squares regression were compared using a paired *t* test. Linear correlation was used to examine the relationship between time to eye opening on command and the duration of infusion.

Results

Demographic data of the patients in the two phases of the study are listed in Table 7.1.

TABLE 7. 1. *Patient demographic data, mean (range).*

	Age (yr)	Weight (kg)	Sex M/F	Duration of infusion (min)
Part 1 (n=10)	5.2 (4 - 7)	18 (15 - 22)	6/4	38 (18 - 108)
Part 2 (n=20)	6.8 (4 - 10)	23.7 (15 - 43)	19/1	30 (18 - 56)

In the first part of the study a total of 67 blood samples were obtained from the 10 patients. The target concentrations of propofol for satisfactory anaesthesia ranged from 5 - 13 $\mu g.ml^{-1}$. The mean total dose of propofol administered was 372 mg (range 263 - 563 mg) and the mean rate of infusion was 29.8 $mg.kg.^{-1}h.^{-1}$(range 13.5 - 46.6 $mg.kg.^{-1}h.^{-1}$). The precision of the model was 24.8% and bias -18.5%. After the iterative linear least-squares regression procedure, the revised pharmacokinetic variables had a theoretical precision of 23.1% and bias of -0.3% (Table 7.2). Fit of the model was significantly improved ($p<0.001$). Mean time to eye opening on command after cessation of infusion, was 35 minutes (range 19 - 68 min).

TABLE 7.2. *Initial and revised rate constants for propofol using a three compartment open model for patients in the first part of the study, and prospective evaluation of the revised rate constants.*
Numbers in parentheses are the range for individual patients.

	Initial	Revised	Prospective testing of revision
V_c (ml.kg^{-1})	343	432	432
k_{10} (min^{-1})	0.1000	0.0967	0.0967
k_{12} (min^{-1})	0.0855	0.1413	0.1413
k_{13} (min^{-1})	0.0210	0.0392	0.0392
k_{21} (min^{-1})	0.0330	0.1092	0.1092
k_{31} (min^{-1})	0.0033	0.0049	0.0049
Bias (%)	-18.5 (-41.2 to 10.4)	-0.3 (-28.9 to 28.6)	-0.1 (-30 to 42)
Precision (%)	24.8 (6.5 to 41.2)	23.1 (8.2 to 31.8)	21.5 (8.4 to 43.1)
Precision in individuals during infusion			11.9 (3.2 to 30.1)

During the second part of the study, a total of 177 blood samples were taken from the 20 patients. Mean duration of surgery was 32 min (16 - 65 min). The mean propofol infusion rate was 28.4 mg.kg.$^{-1}$h.$^{-1}$ (range 7.5 - 44.2 mg.kg.$^{-1}$h.$^{-1}$). The mean target concentration for maintaining satisfactory anaesthesia during the infusion phase was 6.6 μg.ml^{-1} (range 3 - 11 μg.ml^{-1}) and the mean total dose of propofol given was 409 mg (range 222- 797 mg).

Precision of the revised model was 21.5% and bias -0.1% (Table 7.2). The correlation between measured and predicted propofol concentrations is displayed in Figure 7.1 (r = 0.86, p = 0.0001), and the relationship between the predicted blood concentration and predicted error is shown in Figure 7. 2.

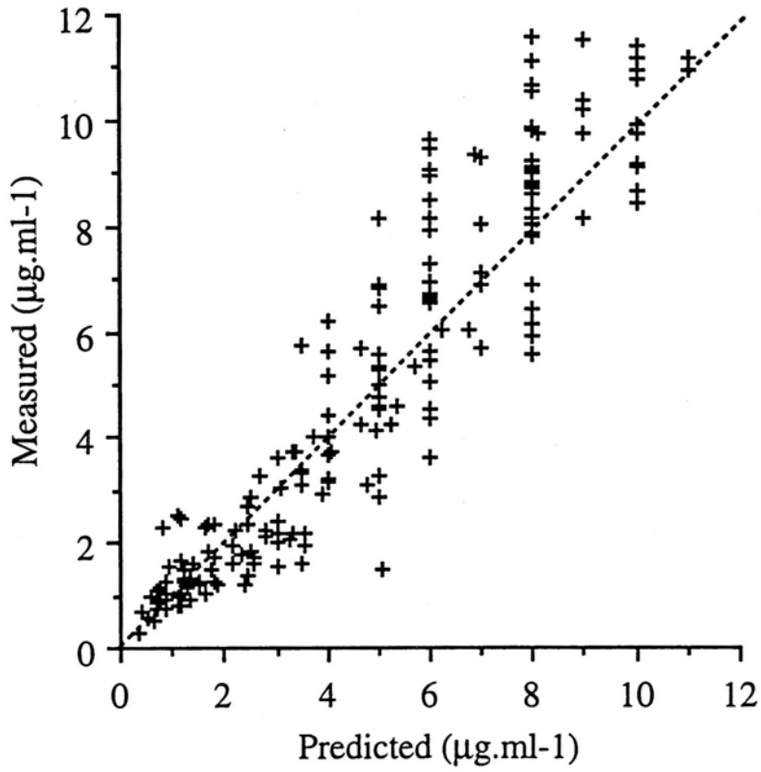


FIGURE 7. 1. Correlation between predicted and measured blood propofol concentrations, n = 177, r = 0.86. (From Short *et al*, 1994)

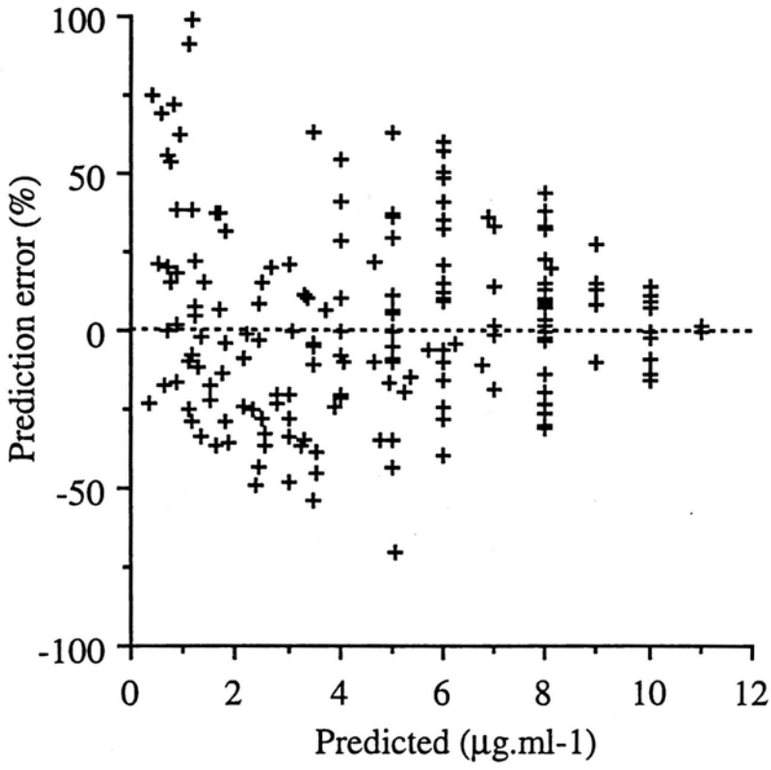


FIGURE 7.2. Comparison between predicted blood concentrations of propofol and prediction error, n = 177. (From Short et al, 1994)

The individual prediction errors are displayed over time in Figure 7.3. Individual data are listed in Appendix C (page 213) Precision in individual patients during the infusion phase was 11.9% (range 3.2 to 30.1%). This indicates that the model was better at maintaining a constant plasma concentration than predicting what that plasma concentration would be. Further iterative-linear least squares regression of the pharmacokinetic variables did not result in a further theoretical improvement in bias or precision of the model.

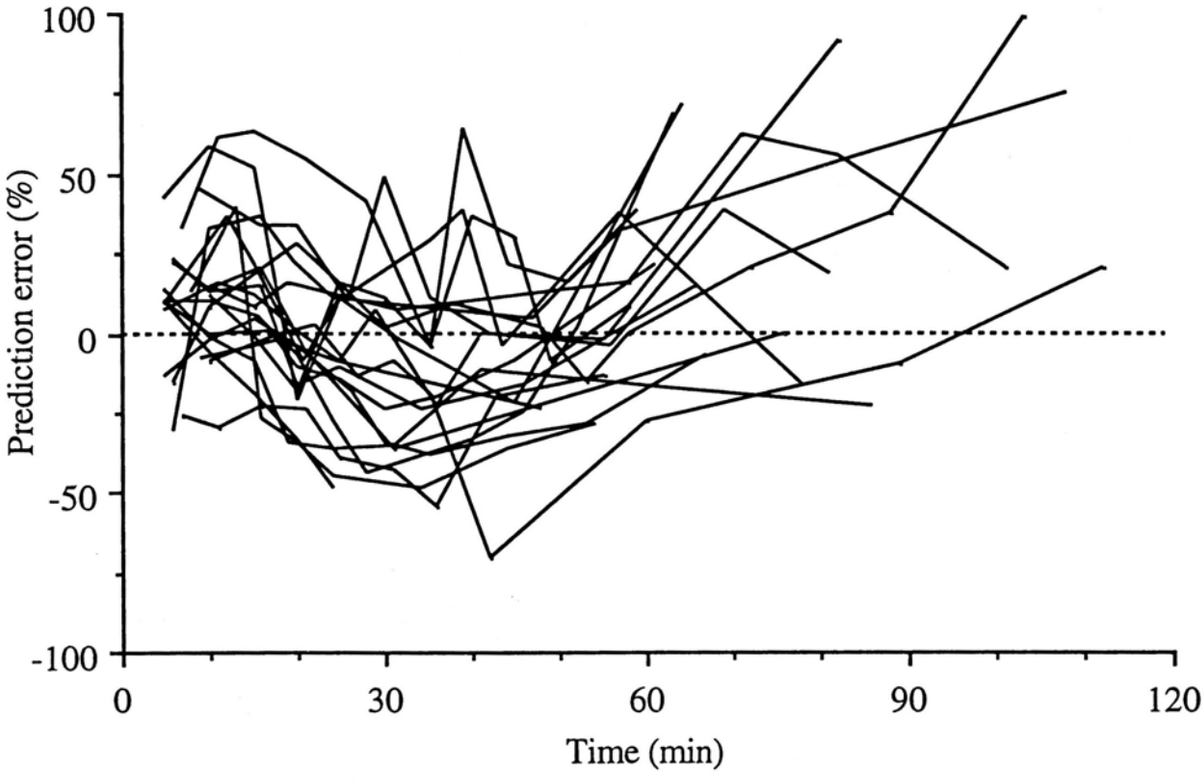


FIGURE 7. 3. Individual prediction errors over time. (n= 20).

In the second phase of the study, the mean time to eye opening on command after termination of the infusion and nitrous oxide was 40 min (17 - 80 min) and did not correlate with the duration of infusion ($r = -0.2$, $p = 0.2$) . Predicted blood concentration at this time was 0.86 $\mu g.ml^{-1}$ (range 0.40-1.45 $\mu g.ml^{-1}$). Four patients had an increase in blood propofol concentration in the last blood sample, obtained between 52 and 103 minutes after cessation of the infusion. The magnitude of the increase was between 7 - 21% and occurred at blood concentrations between 0.83 and 2.50 $\mu g.ml^{-1}$.

Discussion

Compared with the original study by Marsh and colleagues [1991], the precision of the pharmacokinetic model-controlled infusion evaluated was lower (24.8% vs 20.1%) and there was a large bias (-18.5%) in the results. This means that the algorithm overpredicted the measured plasma concentrations by 18.5% indicating that the pharmacokinetic data by Marsh and colleagues were not applicable in the local Chinese paediatric population. This model had been developed using children of similar ages and undergoing similar procedures to the patients in this study. The revised pharmacokinetic parameters were found to fit the 20 patients well on prospective evaluation in the second phase of study suggesting a difference in the pharmacokinetic profiles of children in the two studies. The infusion system using the kinetics by Marsh and colleagues [1991] has been reported to be satisfactory in a recent propofol infusion by Doyle and colleagues in Glasgow [1993].

The reasons for the difference in pharmacokinetic variables are unclear. Possible differences between the studies included the difference in the ethnic origin of the patients, no sedative premedication in this study, and the local regional block being performed at the end of surgery

rather than at the beginning, in the first part of the study. The central volume of distribution in this study was 25% larger than that of Marsh and colleagues. However, caution must be exercised in interpreting the pharmacokinetic parameters in the model after it has been subjected to an iterative least-squares regression procedure, because the relative contribution of each of the variables to the overall model is influenced by its order in the regression procedure. The revised model is regarded best as a mathematical algorithm that best fits the blood concentration-time profile of the drug, rather than a true-compartmental pharmacokinetic model.

The measured blood levels from the 20 patients in the second part of the study were correlated with the theoretical predicted propofol levels based on the infusion models of pharmacokinetic sets obtained from (1) the bolus kinetic study in Chapter 6 (page 92), (2) the study by Jones and colleagues [1990] and (3) that by Kataria and colleagues (naive pooled approach) [1994]. All the parameter sets underpredicted the measured blood concentrations (Figures 7.4, 7.5, 7.6)

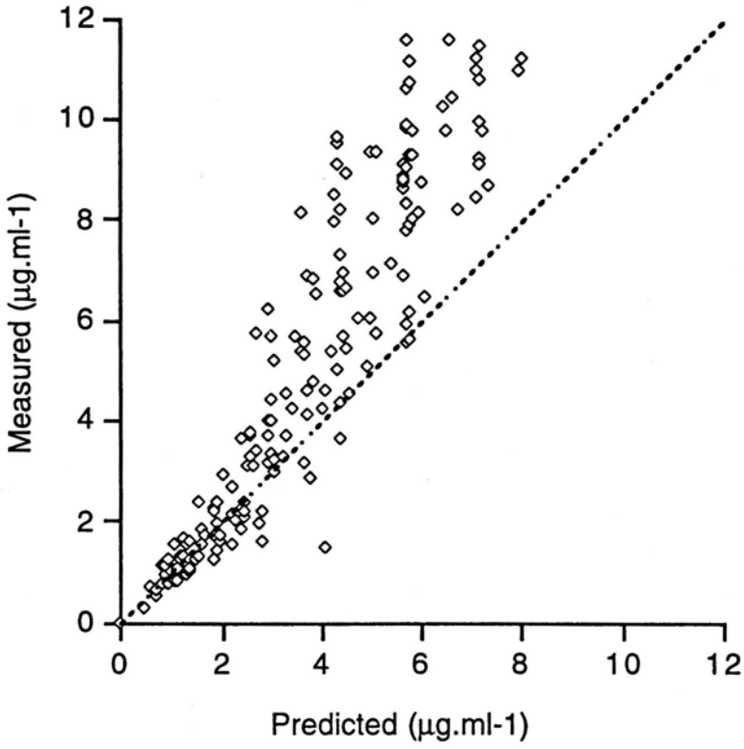


FIGURE 7.4. Correlation between measured and predicted blood concentrations using the bolus kinetics from Chapter 6, r = 0.8.

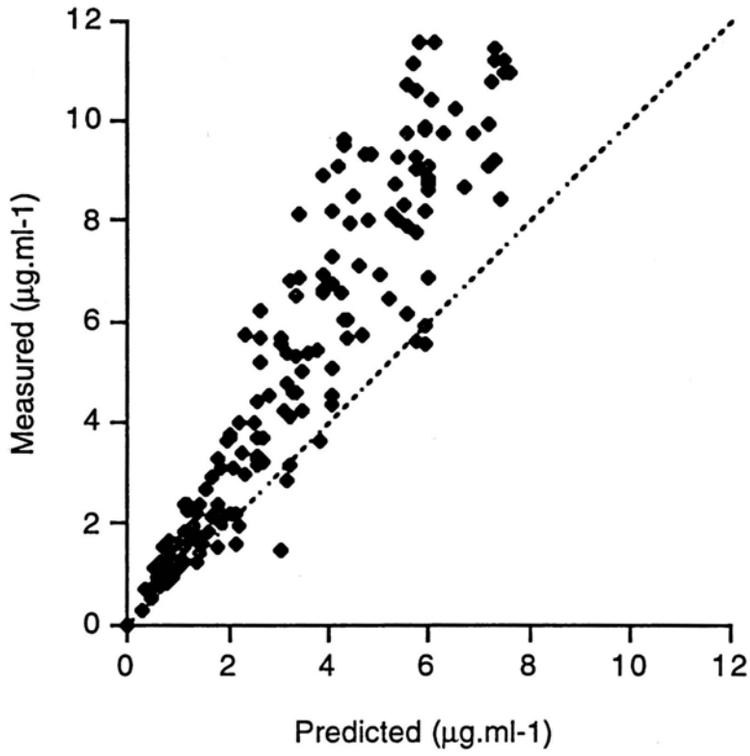


FIGURE 7.5. Correlation between measured and predicted blood concentrations using the bolus kinetics from Jones' study [1990], r = 0.9.

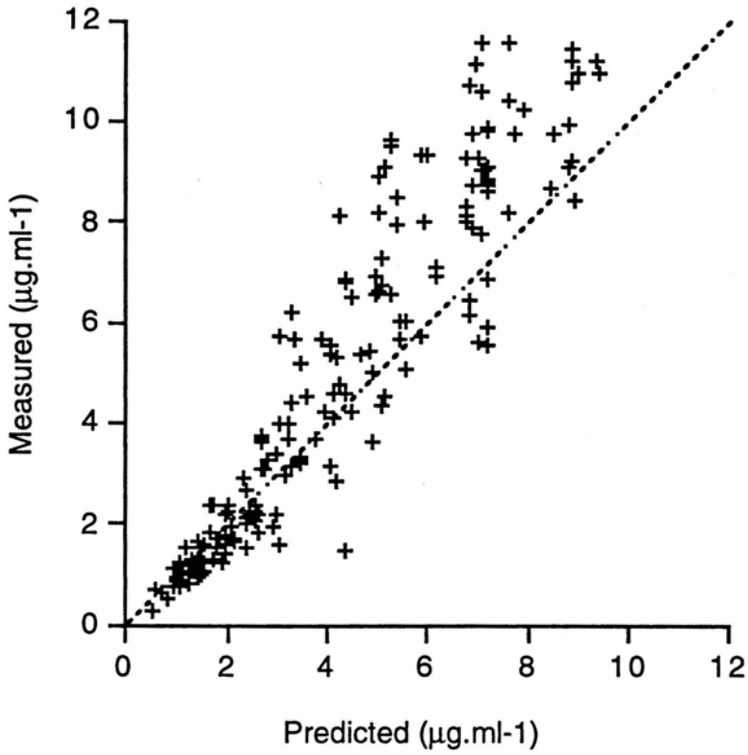


FIGURE 7.6. Correlation between measured and predicted blood concentrations using the mixed kinetics from Kataria's study [1994], r = 0.9.

The theoretical bias and precision were also calculated from these studies and are tabled. The set from Kataria and colleagues has a smaller bias and precision than those from the two bolus studies (Table 7.3). This finding emphasizes the unreliability of using the pharmacokinetic data derived from single dose kinetic studies to predict infusion regimens.

TABLE 7.3. *Bias and precision of the paediatric pharmacokinetic parameters applying on the measured blood concentrations of the 20 patients in the second phase study.*

	Current (infusion)	Current (bolus)	Kataria et al (bolus and infusion)	Jones et al (bolus)
Vc (ml.kg $^{-1}$)	432	660	520	597
k_{10} (min^{-1})	0.0967	0.0779	0.0660	0.1060
k_{12} (min^{-1})	0.1413	0.1237	0.1130	0.0965
k_{13} (min^{-1})	0.0392	0.0490	0.0510	0.0470
k_{21} (min^{-1})	0.1092	0.1020	0.0590	0.0810
k_{31} (min^{-1})	0.0049	0.0116	0.0032	0.0092
Bias (%)	1.74	28.16	11.78	50.86
Precision (%)	21.57	37.34	25.93	52.61

The large infusion rates required for satisfactory anaesthesia in the first part of the study, when no local anaesthetic block had been performed were of concern. The mean infusion rate of 29.8 mg.kg^{-1}.h^{-1} was 50% higher than the ED_{95} of 20.9 mg.kg^{-1}.h^{-1} found in adult patients who had been premedicated with lorazepam [Turtle *et al*, 1987] and, it is two and half times higher than the ED_{95} of 10.5 mg.kg^{-1}.h^{-1} in children who had a supplement of alfentanil at a mean plasma concentration of 135 ng.ml^{-1} [Browne, Prys-Roberts, and Wolf, 1992]. The intralipid load at

this infusion rate was 0.32 $g.kg^{-1}.h^{-1}$ which is close to the recommended maximum infusion rate for intralipid of 0.5 $g.kg^{-1}.h^{-1}$. When using propofol for infusion, one should consider the use of the 2% propofol solution rather than the usual 1% solution.

The concept of balanced anaesthesia in total intravenous anaesthesia uses a combination of drugs to achieve a desired anaesthetic effects with suppression of stress response without cardiovascular depression [Savege, 1979]. Propofol is the only drug currently available which fulfills the qualities of the hypnotic component in total intravenous anaesthesia. An opioid is usually required to suppress the reflex response to noxious stimuli. An alternative approach avoiding opioids would be to use local anaesthesia to block the noxious stimuli. This gives the benefit of providing postoperative analgesia without the risk of respiratory depression in the recovery phase. This is particularly useful in paediatric anaesthetic practice. It was surprising to observe that the infusion rates required in the first part of the study (29.8 $mg.kg.^{-1}h^{-1}$) were reduced only slightly by performing a local anaesthetic block before surgery (28.4 $mg.kg.^{-1}h^{-1}$). The same pharmacokinetic model controlled infusion was used in a further 18 patients making a total of 38 patients to complete the pharmacodynamic study. This aspect will be described in Chapter 8 (page 132). The mean infusion rate in the 38 patients was 27.3 $mg.kg.^{-1}h^{-1}$ (range 7.6 - 44.5 $mg.kg.^{-1}h^{-1}$). It is not sure why there was not a greater reduction in the mean infusion rate required. One possible explanation is that the surgery was commenced before the block was effective. A large part of the propofol dose would have been administered already by this stage. The regional block may be inadequate to block the response to the surgical stimuli, although the majority of the children appeared to be pain free in the recovery period.

The initial recovery was slow after cessation of infusion. The reasons for the slow recovery include the more than seven fold difference in the mean theoretical concentration required to maintain anaesthesia (6.6 $\mu g .ml^{-1}$) and the mean predicted concentration at which eye opening to command (0.86 $\mu g .ml^{-1}$) occurred in this series of patients. The decay in plasma concentration after cessation of the infusion was prolonged even after the brief surgical procedures in this study. This point is demonstrated in the modelling of the decay curve of blood propofol concentration using mean data from the second part of this study (Figure 7.7).

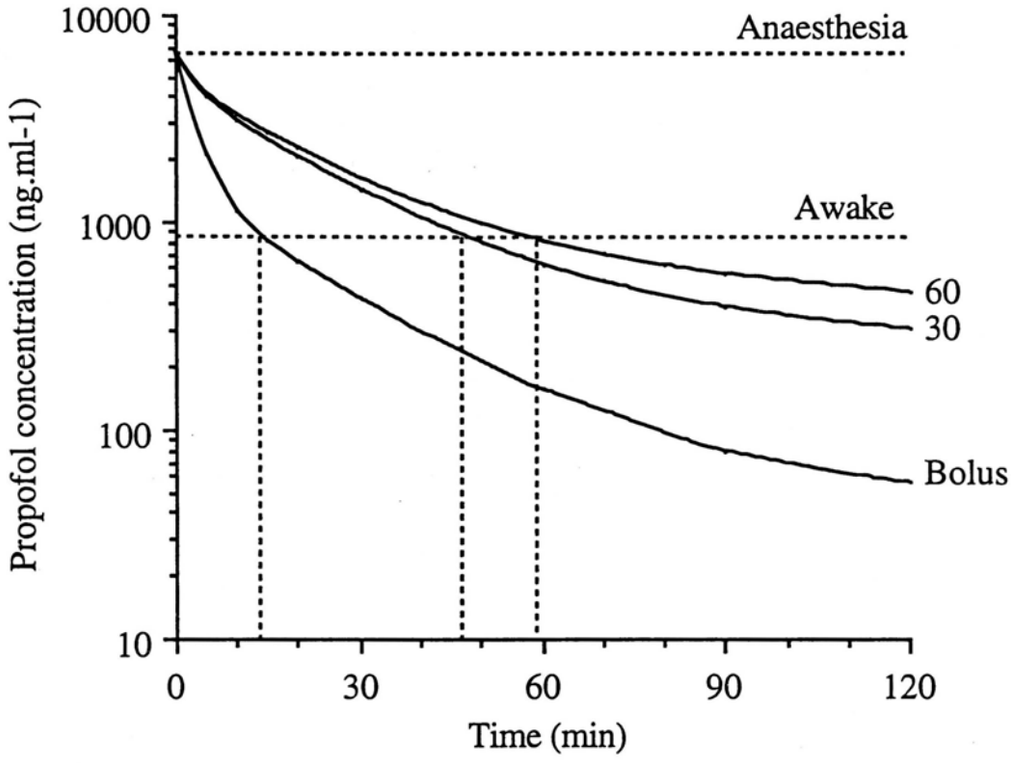


Figure 7.7. Modelling of the decay in blood concentration of propofol after cessation of an infusion to maintain a constant blood concentration of 6.6 μg ml^{-1} for 30 minutes and 60 minutes, and of a bolus dose which may attain this concentration (2.85 $mg.kg^{-1}$). The dashed lines correspond to the mean blood concentration of propofol required to maintain satisfactory anaesthesia and that at which eye opening to command occurred. (After Short et al, 1994)

A bolus dose which attains a blood concentration of 6.6 μg $.ml^{-1}$ (2.85 $mg.kg^{-1}$) and infusions to maintain blood concentrations at 6.6 μg $.ml^{-1}$ for 30 min and one hour are displayed. It took 48 minutes in the case of 30 minute infusion and 59 minutes in the case of 60 minute infusion to reach 0.86 μg $.ml^{-1}$ blood propofol concentration. A blood concentration of 6.6 $\mu g.ml^{-1}$ was chosen because it was the mean blood concentration required during the infusion phase of the study. The mean predicted concentration of 0.86 μg $.ml^{-1}$ at which eye opening occurred

was slightly lower than the concentration of 1.4 μg .ml^{-1} in a similar study [Doyle, McFadzean, and Morton, 1993]. However, both these figures were predicted values. In an earlier paper [Vandermeersch *et al*, 1989], using a continuous infusion of propofol at a rate of 12 mg.kg.$^{-1}$h.$^{-1}$ in children of similar age, the mean concentration of propofol measured was 2.32 μg .ml^{-1} at the time of awakening. These patients were heavily premedicated with hyoscine and morphine, and fentanyl had been given intraoperatively. The patients took 39.6 (SD 12.6) minutes to wake up.

Secondary peaks of propofol concentration were observed in four patients during the early recovery period. The incidence might have been higher if sampling had been carried out in the late recovery period. However sampling was performed only during the early recovery period because of the concern over the number of blood samples taken and because the objective of this study was to examine the accuracy of the algorithm during the infusion and the early recovery phase. The blood concentrations of propofol obtained during these peaks ranged between 0.83 and 2.5 μg .ml^{-1}, which exceeded the predicted concentration for eye opening on command. This indicates that there is a need for prolonged observation of these patients as there is a possibility that clinically significant resedation could occur. Secondary peaks after propofol bolus doses have been previously observed in children as well as in adults [Jones, Chan, and Andrew, 1990; Gin *et al*, 1990].

In summary, maintenance of anaesthesia using propofol by means of a pharmacokinetic-controlled infusion system is feasible in children provided the algorithm used is accurate for the population concerned.

SECTION IV
ANAESTHESIA AND RECOVERY

CHAPTER 8

Comparison of Anaesthesia and Recovery of Four Anaesthetic Techniques

COMPARISON OF ANAESTHESIA AND RECOVERY OF FOUR ANAESTHETIC TECHNIQUES

Introduction

There has been much interest in the recovery profile of propofol anaesthesia in children. Many studies have compared propofol either as an induction agent or as a total anaesthetic with various combination of thiopentone, halothane or isoflurane. [Mirakhur, 1988; Puttick and Rosen, 1988; Valtonen *et al*, 1988; Borgeat *et al*, 1990; Larsson, Asgeirsson, and Magnusson, 1992; Martin, Nicolson, and Bargas, 1993; Runcie *et al*, 1993; Weir *et al*, 1993]. Most of these studies compare two methods at a time.

One of the attributes of an intravenous anaesthetic agent as a component in total intravenous anaesthesia is that the recovery after the end of surgery should compare well with other conventional techniques [Booker, 1989].

In this study, the anaesthetic and recovery characteristics of propofol infusion for induction and maintenance of anaesthesia were compared simultaneously with three established anaesthetic techniques, propofol, thiopentone or halothane for induction followed by halothane maintenance in children undergoing minor surgical procedures.

Methods

This study was performed on 163 healthy Chinese children aged between three and 12 years scheduled for body surface surgery estimated to take less than one hour, and where a regional anaesthetic block could be performed for analgesia. Children who were uncooperative, unable to perform a simple child's puzzle, had a history of halothane anaesthesia within the previous three months, allergy to any of the study medications, or a previous adverse reaction to anaesthesia were excluded. Children in the study were randomly assigned to one of four groups:

1) PP group - propofol by infusion for induction of anaesthesia, maintenance of anaesthesia with propofol infusion and 70% nitrous oxide in oxygen.

2) PH group - propofol for induction, maintenance of anaesthesia with halothane and 70% nitrous oxide in oxygen.

3) TH group - thiopentone for induction, maintenance of anaesthesia with halothane and 70% nitrous oxide in oxygen.

4) HH group - halothane for induction, maintenance with halothane and 70% nitrous oxide in oxygen.

No sedative premedication was given. EMLA cream was applied over the back of both hands approximately one hour before the time of anaesthesia to assist with the intravenous insertion of the cannula.

In group PH and group TH, anaesthesia was induced with bolus doses of propofol (2.5 $mg.kg^{-1}$) and thiopentone (4.0 $mg.kg^{-1}$) respectively. Increments were given if necessary up to 1 $mg.kg^{-1}$. Anaesthesia was maintained with halothane 1-2% and 70% nitrous oxide in oxygen. In group HH, anaesthesia was induced and maintained with halothane 1-3% and 70% nitrous oxide in oxygen. In group PP, anaesthesia was induced and maintained with propofol by continuous intravenous infusion using the pharmacokinetic model controlled infusion pump. The details are described in the method chapter (page 45) and Chapter 7 (page 111). The target

concentration of propofol in the blood was initially set at 8 $\mu g.ml^{-1}$ at induction and subsequently the concentration was adjusted according to standard clinical criteria to maintain an adequate level of anaesthesia. In group PP, the induction dose of propofol was calculated from the theoretical target blood concentration (8 $\mu g.ml^{-1}$) and the revised central volume of distribution (432 $ml.kg^{-1}$) obtained from the infusion study (Chapter 7, page 111). The mean infusion rate was derived by dividing the total propofol maintenance dose by the duration of anaesthesia. The 20 patients in the second part study of the pharmacokinetic model controlled infusion of propofol (page 111) are included in the assessment in this study.

Lignocaine 2% in a dose of 0.2 $mg.kg^{-1}$ intravenously was given just before the administration of propofol in the PP and PH groups to reduce pain on injection. A Rees modification of Ayres T-piece and laryngeal mask airway was used for children who weighed less than 20 kg. A Magill system was used in those above this weight. The quality of the anaesthetic induction was graded as good (induction uneventful), adequate (presence of minor side effects which did not interfere with induction), or poor (presence of severe side effects which caused a difficult induction).

The depth of anaesthesia in all patients was adjusted according to standard clinical criteria to prevent movement in response to surgical stimuli and to maintain arterial pressure and heart rate within 20% of baseline. Analgesia was provided by an appropriate regional nerve block and rectal paracetamol 10-20 $mg.kg^{-1}$ given immediately after induction of anaesthesia. Arterial oxygen saturation, noninvasive arterial pressure, heart rate and capnometry were monitored throughout the procedure. All anaesthetic agents were discontinued at the same time at closure of the surgical incision. The laryngeal mask was removed at this time.

Recovery was assessed by the recovery room nurses who were unaware of the anaesthetic technique used. The followings were recorded:

(1) time from the end of anaesthesia (discontinuation of anaesthetic agents) to achieving a full Steward score [Steward, 1975] (0, 1, or 2 points were given to each of the three categories; conscious level, airway control, and movement. The maximum possible score is 6);

(2) time from the end of anaesthesia to opening eyes and other simple activities on command; and

(3) time from end of anaesthesia to orientation (able to tell name and age correctly). Psychomotor recovery was assessed by a simple child's jigsaw puzzle. The puzzle consisted of six different shapes and colours which needed to be placed in the appropriate places. All children were trained before the anaesthetic, by a research nurse who was not involved in the management of anaesthesia. The shortest time of three attempts to complete the task was recorded as the preoperative baseline time. This test was repeated at 30 minutes, one hour and two hours after anaesthesia. All side effects and adverse reactions during the study period were recorded. Rescue analgesia consisted of a parenteral opioid as prescribed by the anaesthetist concerned.

Statistical analysis

The demographic data were compared using analysis of variance (ANOVA) and preoperative psychomotor test data were compared with the chi-square test. The postoperative psychomotor test data were analysed using a k - sample Van der Waerden test. In this test, the times taken to complete the puzzle were ranked according to their values. Highest possible ranks were given to those cases who could not perform the test because of sedation. The ranks were then transformed into normal scores for the analysis. Significant results from the ANOVA and nonparametric k-sample test were further compared using Dunnett's *t* test or 2-sample Van der Waerden test with adjustments to the p-values where appropriate. The

differences between the preoperative and the postoperative psychomotor data were compared by the Wilcoxon sign rank test.

Results

Data from five cases were excluded from the analysis because these children required opioid administration to relieve their postoperative pain before the end of the study period. Patient data were similar in the four groups (Table 8.1). Individual demographic data are listed in Appendix C (page 216) . Anaesthesia details and side effects are listed in Table 8.2.

TABLE 8.1. *Patient demographic data, (Mean (range))*

	PP (n=38)	PH (n=42)	TH (n=39)	HH (n= 39)
Age (yr)	6.7 (3-10)	6.9 (3-12)	6.5 (3-11)	6.4 (3-11)
Sex (M/F)	34/4	32/10	33/6	30/9
Weight (kg)	23.2 (14-44)	23.4 (12-56)	21.2 (13-46)	22.3 (14-33)

Duration of anaesthesia was similar at about half an hour in the four groups. In group PP, the mean induction dose was calculated as 3.5 $mg.kg^{-1}$ and the mean infusion rate of propofol was 27.3 (SD 8.1) $mg.kg.^{-1}\ h^{-1}$ (range 7.6 to 44.5 $mg.kg.^{-1}\ h^{-1}$). In group PH, the mean induction dose was 2.9 (SD 0.8) $mg.kg^{-1}$. The mean dose of thiopentone in group TH was 4.7 (SD 0.6) $mg.kg^{-1}$. There were no statistical differences in the grading of quality of anaesthetic induction between the groups ($p = 0.114$). During induction, pain on injection was only observed in groups PP (18.4%) and PH (14.3%). Apnoea was significantly more frequent in the PP group ($p=0.001$). Eighteen patients (47.4%) in group PP, nine patients (21.4%) in group PH, seven patients (17.9%) in group TH and only one patient (2.5%) in group HH were

apnoeic for longer than 20 s after induction. The lungs of one child in group PP had to be ventilated by hand throughout the procedure because of the apnoea, yet the child moved in response to surgical pain on several occasions after attempts to decrease the infusion rate. Breath holding was observed in one case in the HH group. There was no significant difference in the other respiratory side effects. Involuntary movements were noted in the three groups using an intravenous agent (PP, PH, and TH), and were more frequent with propofol than with thiopentone ($p=0.001$). This occurred in 13 patients (34.2%) in group PP, 19 patients (45.2%) in group PH, nine patients (23.0%) in group TH, and none in group HH.

Intraoperatively, respiratory complications were more common in group PP. In the child who desaturated, this was related to the apnoeic spells and the patient's lungs had to be hand-ventilated most of the time. Arrhythmias were noted in groups TH and HH but none occurred in propofol groups (Table 8.2). However none of these complications was serious enough to interfere with the progress of surgery.

TABLE 8.2. *Anaesthesia details and side effects in the four groups (mean (SD) or number)*

	PP (n= 38)	PH (n=42)	TH (n=39)	HH (n=39)
Duration (min)	31.3(10.2)	31.9(9.8)	31.8(15.3)	34.2(13.6)
Induction Quality				
Good	18	23	24	29
Adequate	14	18	13	9
Poor	5	1	2	1
Apnoea > 20s	18**	9	7	1
Cough	1	1	5	2
Laryngeal spasm	1	0	1	1
Involuntary movements	13**	19**	9	0
Pain on injection	7	6	0	-
Intraoperative problems				
Arrhythmia episodes	0	0	4	5
Apnoea	2	0	0	0
Cough	1	0	0	0
Laryngeal Spasm	2	0	0	0
Desaturation	1	0	0	0

** $p < 0.05$, ** $p < 0.01$*

TABLE 8.3. *Recovery times from the end of anaesthesia for various objectives (mean (SD))*

	PP (n=38)	PH (n=42)	TH (n=39)	HH (n= 39)
Full Steward score (min)	40.6 (13.4)**	22.9 (9.6)	23.8 (10.9)	19.8 (7.8)
Open eyes on command (min)	39.8 (12.9)**	21.9 (9.9)	23.4(11.3)	20.1 (8.9)
Orientation (min)	41.3 (13.7)**	22.3(8.7)	24.8 (11.0)	21.8 (10.9)

** $p < 0.01$

Recovery times of the four groups are shown in Table 8.3. After operation, children in group PP were slower to wake up. Times from the end of anaesthesia to achieving all recovery objectives (full Steward score, open eyes on command, and orientation in name and age) were significantly longer for the group PP compared with those for the other three groups (p= 0.0001). Recovery times in the groups PH, TH, and HH were similar. In group PP, the calculated mean propofol concentration at the end of infusion and anaesthesia was 4.9 (range 2.5 to 8.0) $\mu g.ml^{-1}$, and at the time of opening eyes on command was 0.97 (range 0.4 to 1.9) $\mu g.ml^{-1}$, and at the time of orientation was 0.9 (range 0.5 to 1.5) $\mu g.ml^{-1}$.

The mean times taken to perform the puzzle before operation were similar in the four groups (p=0.851). After anaesthesia, there was impairment in psychomotor performance in all four groups, and the times taken to complete the puzzle at all time points were significantly longer than before operation (p=0.0001). The performance by group PP was the worst in terms of the number of patients who were able to do the puzzle and the time

required to complete the task at 0.5 hour (p=0.0001) and at 1 hour (p=0.024) after anaesthesia. Group PH scored best, but not significantly better than groups TH and HH. Although the difference between all four groups had disappeared by two hour time, there was still 22-28% impairment in performance compared to baseline (Table 8.4).

TABLE 8.4. *Psychomotor test : preoperative and the postoperative times required to perform the puzzle (mean (SD))*

	PP (n=38)	PH (n=42)	TH (n=39)	HH (n=39)
Preoperative Time required (s)	20.6 (13.4)	21.2 (11.5)	22.2 (9.8)	22.8 (11.3)
0.5 h after anaesthesia % of children able to perform test	28.3	88.1	71.8	76.9
Time required (s)	43.3 (15.3) **	29.7 (11.3)	36.0 (17.1)	32.3 (16.2)
1 h after anaesthesia % of children able to perform test	87.2	97.6	97.4	94.9
Time required (s)	31.7 (12.1)*	27.2 (13.6)	29.1 (10.9)	30.5 (12.7)
2 h after anaesthesia % of children able to perform test	100	100	92.3	92.3
Time required (s)	25.2 (11.7)	26.5 (13.3)	27.6 (12.0)	29.3 (11.2)

* $P < 0.05$, ** $p < 0.01$.

The postoperative side effects are listed in Table 8.5. Group PH had the least problems. The incidence of restlessness and disorientation was greater in group PP. More children in groups TH and HH complained of giddiness. The incidence of nausea and vomiting was zero in the PP group and greatest in group HH with groups PH and TH intermediate. Statistical analysis was not carried out on side effects as their incidence was too small.

TABLE 8.5. *Postoperative complications (number of patients)*

	PP (n=38)	PH (n=42)	TH (n=39)	HH (n=39)
Giddiness	0	0	8	6
Drowsiness	1	1	1	4
Restlessness /disorientation	3	0	1	1
cry/uncooperative	3	1	5	3
Headache	0	0	0	2
Nausea/vomiting	0	1	1	7

Discussion

A comparison of anaesthetic techniques should be performed ideally with a similar level of anaesthesia. However, there are still many limitations to the objective monitoring of central nervous system sedation especially in paediatric practice. The criteria used in this study were the standard clinical criteria similarly used in other paediatric studies to maintain a comparable level of anaesthesia between the groups [Martin, Nicolson, and Bargas, 1993; Hannallah *et al*, 1994]

In group PP, an initial blood target propofol concentration of 8 $\mu g.ml^{-1}$ was set for induction of anaesthesia. This was based on the findings (concentration range of 5-13 $\mu g.ml^{-1}$) from the pilot study of 10 cases in the pharmacokinetic-model-controlled infusion study (page 111). The quality of induction was not different from the other three groups ($p=0.114$). Respiratory side effects were more frequent in group PP during induction as well as during operation. This may be due to the difficulty in maintaining an optimum level of anaesthesia with a new technique. The use of propofol infusion for maintenance of anaesthesia is still new in paediatric practice. The incidence of pain on injection in this study is smaller than that in the dose requirement study (page 52) suggesting that the lignocaine dose used in this study (0.2 $mg.kg^{-1}$) is more effective than the dose used in that study

(0.15 mg per 3 mg of propofol). Dose of 0.2 $mg.kg^{-1}$ lignocaine is the minimum effective dose recommended [Morton *et al*, 1992]. The incidence of involuntary movements following propofol induction (35% in PP to 45% in PH) was more frequent compared with thiopentone induction (23%). However these were transient and did not disrupt the surgical procedure. The absence of arrthymias in groups PP and PH is encouraging. However the sample studied is probably not large enough to make any definite conclusion on this finding.

Recovery was significantly slower in group PP compared with the other three groups. The children took twice as long to achieve the recovery objectives (Table 8.3). This was both statistically and clinically significant. This finding is in contrast to the other paediatric studies [Puttick and Rosen, 1988; Borgeat *et al*, 1990; Doyle, McFadzean, and Morton, 1993; Martin, Nicolson, and Bargas, 1993; Hannallah *et al*, 1994]. Puttick and Rosen [1988] and Borgeat and associates [1990] observed a faster recovery following propofol anaesthesia compared with thiopentone induction and halothane maintenance in dental and ENT patients respectively. Martin and colleagues [1993] and Hannallah and coworkers [1994] reported no difference in the recovery time after anaesthesia with total propofol anaesthesia compared with the other anaesthetic techniques used in their studies. However the methodology used in these studies were different from the current study. In the studies by Martin and colleagues [1993] and Borgeat and associates [1990], patients' lungs were ventilated after neuromuscular blockade. Patients in Hannallah's study [1994] had their trachea intubated and some had non-depolarising neuromuscular blockade during the procedure. Puttick and Rosen [1988] used intermittent boluses of propofol during maintenance of anaesthesia and the duration of the procedures was less than 10 minutes. The propofol infusion technique used by Doyle, McFadzean, and Morton [1993] was remarkably similar to that in group PP in this study

except for the difference in pharmacokinetic model used. They observed no difference in the recovery times after anaesthesia using either propofol infusion or propofol bolus followed by maintenance with halothane. In contrast, the propofol infusion group in this study took twice as long as the propofol bolus group to recover.

In the study by Doyle and colleagues [1993], the initial target blood concentration of propofol set at induction was in the range of 8-14 $\mu g.ml^{-1}$, and the concentration in this study was set at 8 $\mu g.ml^{-1}$ and then adjusted accordingly. The mean total dose used in their infusion group was 17.9 (range 4.8-28.3) $mg.kg^{-1}$ [Morton-personal communication] which was similar to the 17.1 (range 10-31.9) $mg.kg^{-1}$ used in group PP in this study. Their mean target blood concentration at the end of anaesthesia was 5.8 (range 4-10) $\mu g.ml^{-1}$ [Morton-personal communication] which was slightly greater than the concentration of 4.9 (range 2.5-8) $\mu g.ml^{-1}$ in the present study. The estimated blood propofol concentration at the time when their patients woke up was 1.4 (range 0.3-2.6) $\mu g.ml^{-1}$. This was again slightly greater than that in this study (0.97 (range 0.4-1.9) $\mu g.ml^{-1}$). The patients in the PP group of this study required 39.8 (range 15-70) min to open their eyes on command whereas the children in the study by Doyle and colleagues required only 13.5 (range 4-36) min to wake up and open their eyes spontaneously [1993]. The pharmacokinetic model developed for the local Chinese children had a 25% larger volume of distribution than the model developed in Glasgow [Marsh *et al*, 1991]. This indicates that patients in the current study were maintained at lower plasma concentrations than the patients in the study by Doyle and colleagues [1993]. Therefore, the difference in recovery was not caused by excessive doses of propofol being given to patients in the present study. However the difference in recovery time cannot be fully explained by the pharmacokinetic differences between the two groups and it is possible that there is an ethnic difference in the

pharmacodynamic profile of the drug in the two populations. This suggestion is supported by the longer time required by the patients in this study to recover following propofol induction and halothane maintenance (21.9 min) compared with those patients who had a similar anaesthetic in the study by Doyle and colleagues (10.5 min) [1993]. It is worth noting that delayed recovery has been listed as one of the neurological dysfunction reported after the use of propofol [Committee on Safety of Medicines, 1989]

In an open study of propofol infusion study in Belgium [Vandermeersch *et al*, 1989], recovery was also slow - mean time to open eyes after termination of infusion was 39.5 (SD 12.6) minutes. The mean concentration at the time of awakening was 2.3 $\mu g.ml^{-1}$. This may be related to the difference in the anaesthetic technique used. The patients were heavily premedicated with morphine and hyoscine and intraoperatively, fentanyl was given and the propofol infusion was given at a constant rate of 12 $mg.\ kg.^{-1}h^{-1}$ until the end of the procedure.

The three conventional techniques, propofol, thiopentone or halothane induction followed by maintenance with halothane maintenance (groups TH, PH, and HH) had similar recovery characteristics. Recovery appeared to be more dependent on the maintenance agent rather than the induction agent as has been previously observed by Runcie and colleagues [1993] with anaesthesia over 30 minutes duration.

Psychomotor performance using the time to complete a simple puzzle was included in the assessment to compare the recovery of co-ordination ability. Recovery of psychomotor performance in children who had had propofol infusion was significantly slower than those who had had propofol, thiopentone or halothane for induction and maintenance with halothane. Psychomotor tests have not been commonly used in paediatric studies. In this study, they were found to be easy to perform and they discriminate between degrees of sedation better than simple tests based on the state of

consciousness. The psychomotor recovery appeared comparable to previous adult studies [Gregory *et al*, 1990], indicating that recovery from anaesthesia is no faster in children. The children who had had propofol for anaesthesia had a lesser incidence of emesis than those who had had halothane. Many recent studies have noted this similar feature with propofol anaesthesia [Watcha *et al*, 1991; Larsson, Asgeirsson and Magnusson, 1992; Martin, Nicolson and Basgas, 1993; Snellen, Vanacker and Van Aken, 1993; Weir *et al*, 1993; Hannallah *et al*, 1994] They were less giddy and drowsy but notably more children were restless and at times, it was difficult to comfort them. This is similar to the finding by Larsson and colleagues [1992].

In summary, propofol for induction and maintenance of anaesthesia supplemented with nitrous oxide and regional block was unsatisfactory in an unpremedicated local Chinese paediatric population. It was associated with a delayed early recovery postoperatively compared with induction of anaesthesia using propofol, thiopentone or halothane and maintenance with halothane. The recovery profiles were similar in the three groups. However, further modification of the infusion and anaesthetic technique and evaluation is necessary before the place of propofol infusion in paediatric anaesthesia can be determined.

SECTION VI
SUMMARY AND CONCLUSIONS

CHAPTER 9

Summary

SUMMARY

The objective of this thesis was to evaluate the use of propofol in paediatric anaesthesia. The hypothesis that propofol is an effective intravenous anaesthetic agent for induction and maintenance of anaesthesia for short surgical procedures in children was tested.

Pharmacology

Propofol (2,6 diisopropyl phenol) in its new emulsion formulation was introduced to clinical anaesthesia in 1983 for trial purposes. It is an alkylphenol with anaesthetic properties and it is virtually insoluble in water. It was originally solubilized in Cremophor EL, but the association of this solubilizing agent with anaphylactoid reactions led to its withdrawal. The currently available preparation is a 1% w/v in aqueous emulsion containing 10% w/v soybean oil, 1.2% w/v egg phosphatide and 2.25% w/v glycerol. The potency of this formulation is slightly less than the Cremophor formulation (AD_{95} of 2.5 $mg.kg^{-1}$ vs 2.0 $mg.kg^{-1}$ respectively).

Clinical pharmacology

The pharmacokinetic profile of propofol can be described by three exponential functions. A fast distribution from blood to well perfused tissues (α half-life of 2-3 min), a rapid metabolic clearance (β half-life of 0.5-1 h), and a slow return of propofol from the poorly perfused compartment (γ half-life of 4-11 h). The estimated central volume of distribution is large (0.3-0.5 $l.kg^{-1}$). The apparent volume of distribution is two to three times as large as the volume at steady state resulting in a very long terminal half-life. Protein binding is 97-99%. Generally clearance exceeds the estimated hepatic

blood flow suggesting that extrahepatic mechanisms contribute to its clearance.

In healthy adults, bolus doses in the range of 2.0-2.5 $mg.kg^{-1}$ are required for induction of anaesthesia depending on the premedication. It has a rapid but variable onset of action (range 22-125 s). The rapid distribution and elimination contribute to its short duration of action. Recovery occurs 15 - 20 minutes after a single induction dose of propofol and is quicker than after thiopentone. A long terminal half-life indicates that propofol might accumulate when it is administered either by repeated bolus injections or constant rate infusion for anaesthesia or sedation. It is currently the intravenous agent of choice as the hypnotic component of total intravenous anaesthesia. Induction of anaesthesia is usually associated with pain on injection and a few excitatory effects. The depression of the cardiovascular system with propofol is more than with an equipotent dose of thiopentone. The decrease in arterial pressure is approximately 30% after induction with propofol. The baroreflex is reset to allow a slower heart rate despite a decrease in arterial pressure. Respiratory depression following propofol induction is common. The upper airway reflexes are more suppressed than after thiopentone. The incidence of postoperative vomiting is so low that it is suggested that propofol has an antiemetic effect.

Clinical Studies

Induction of anaesthesia - Dose requirements

Studies have shown that children require a larger dose of propofol for induction of anaesthesia than adult patients. The data were mostly from children above three years old. The induction dose required in children was determined by a quantal dose-response study of 300 unpremedicated healthy children divided into three age groups: less than two year old, two to five

years old and six to 12 years old. The ED_{50} and ED_{95} for loss of eyelash reflex and acceptance of a facemask were largest in the group less than two years old, smaller in the group two to five years old and smallest in the group six to 12 years old. The acceptance of facemask was considered to be a satisfactory indicator for smooth transition to maintenance of anaesthesia using inhalational anaesthetic agents. The ED_{95} for this endpoint in the three-age groups in ascending order were 2.88, 2.53, and 2.20 $mg.kg^{-1}$ respectively. The recommended dose for induction in unpremedicated children is in the range of 2.5 to 3.5 $mg.kg^{-1}$, the higher dose range being for younger children with decreasing requirements as the age increases. The induction dose required in children is larger than the dose required for adults (2.0-2.5 $mg.kg^{-1}$).

Induction characteristics - Haemodynamic response

Induction of anaesthesia with propofol has been shown to cause a significant reduction in arterial pressure which was greater than that after thiopentone both in children and in adults. The haemodynamic response to propofol was studied in two studies to examine dose-related changes and the mechanism for the hypotension during induction. The arterial pressure and pulse rate changes in response to different induction doses of propofol were studied in 216 patients from the dose-finding study. The doses studied were 1.6, 1.8, 2.0, 2.2, 2.4, and 2.6 $mg.kg^{-1}$. The mean reduction in arterial pressures was 15% over the first minute and 30% at five minutes after propofol. The mean reduction in pulse rate was 17%. The reduction in arterial pressures and pulse rate were not dose-related. This is different from that observed in adults, but the reason is not clear.

The mechanism for the hypotension following propofol was compared with that after thiopentone using the technique of pulsed Doppler echocardiography in two age-groups of children. Intravenous induction of

anaesthesia in children using propofol was found to cause more cardiovascular depression than that after an equipotent dose of thiopentone. After propofol, the cardiac index was reduced by 10-15% and systemic vascular resistance by 15-19%. The heart rate in younger children was reduced significantly (24%) but remained unchanged in the older children. The baroreceptor reflex appeared to be impaired more in younger children than in older children. This degree of cardiovascular depression is of no clinical significance in healthy children, but potentially dangerous in patients with a compromised circulatory function.

Induction characteristics - Other effects

The incidence of pain on injection was variable and not dose-related. When 0.15 mg of lignocaine was mixed with each 3 mg of propofol before injection in the dose finding study, pain on injection was observed in 0 - 43% of children less than two years old, 9 - 33% of children between two and five years old, and 8 - 35% of children between six and twelve years old. The incidence was reduced to 14 - 18% when 0.2 $mg.kg^{-1}$ of lignocaine was given intravenously just before administration of propofol in the study comparing four techniques of anaesthesia.

The incidence of apnoea was dose related, and also appeared to be age related. Using different doses of propofol in the dose finding study, apnoea occurred in 0 - 29% of children less than two years old, 0 - 42% of children between two and five years old and 6 - 53% of children between six and twelve years old.

The incidence of involuntary movements was high, 44% in children less than two years old, 55% in children between two and five years old and 47% in those between six and 12 years old. However, they were short-lived and did not disrupt the conduct of anaesthesia and surgery.

Single dose pharmacokinetics

Physiological changes in distribution of body water, cardiovascular, hepatic, and renal function during childhood may affect the distribution, metabolism and excretion of drugs. Pharmacokinetics after a single intravenous dose of propofol were studied in 23 children aged between one and 12 years old. There was a large interindividual variation in the pharmacokinetic variables. The mean central volume of distribution was 0.66 (SD 0.23) $l.kg^{-1}$, the mean volume of distribution at steady state was 4.40 (SD 1.78) $l.kg^{-1}$, and clearance 49.96 (SD 20.2) $ml.min^{-1}.kg^{-1}$. There was a good correlation between the body weight and the values of central volume of distribution, volume of distribution at steady state and clearance, but no significant correlation was found between age and any of the pharmacokinetic variables. There was no difference in the protein binding of propofol between children less than three years old and those over (98.8% *vs* 98.6%). This implies that the difference in the propofol dose required for induction of anaesthesia in different age groups of children is not due to age-related differences in pharmacokinetics. The differences may be pharmacodynamic in origin. The central nervous system may have a different sensitivity to anaesthetic agents at different ages. The fact that there is no age-related difference in propofol pharmacokinetic variables from one to 12 years old suggests that the same algorithm can be used for infusion in children within this age range. However, the infusion rate should be titrated against clinical effects because target-concentrations required vary between individuals.

Maintenance of anaesthesia - infusion pharmacokinetics

Compared with thiopentone, propofol has a suitable pharmacokinetic and pharmacodynamic profile for maintenance of anaesthesia by infusion. Infusion of intravenous agents has been simplified by the availability of

computer-controlled infusion pumps controlled by pharmacokinetic models. The use of a published algorithm for administering propofol to paediatric patients was prospectively tested in 10 Chinese patients between four and 10 years old. The precision of the model was 24.8% and bias -18.5%. A revised pharmacokinetic algorithm for this population was developed after iterative linear least squares regression procedure. The revised pharmacokinetic algorithm which had a theoretical precision of 23.1% and bias of -0.3% was evaluated in another sample of 20 paediatric patients. The precision was 21.5% and bias -0.1%. The mean target concentrations of propofol were 5-13 $\mu g.ml^{-1}$. Further iterative linear least squares regression of the pharmacokinetic variables did not result in a further theoretical improvement in bias or precision of the model.

Anaesthesia using propofol infusion for induction and maintenance of anaesthesia by this infusion system was compared with three standard techniques of anaesthesia: propofol, thiopentone or halothane for induction followed by halothane for maintenance in 163 healthy children undergoing minor body surface procedures. All patients breathed 70% nitrous oxide in oxygen spontaneously. Duration of anaesthesia was about half an hour duration. In the propofol infusion group, the mean induction dose of propofol during induction was 3.5 $mg.kg^{-1}$ and the mean infusion rate was 27.3 (SD 8.1) $mg.kg.^{-1}h^{-1}$. The mean induction dose of propofol was 2.9 $mg.kg^{-1}$ in the propofol bolus group, and the induction dose in the thiopentone group was 4.7 $mg.kg^{-1}$. Analgesia was provided by an appropriate regional block. The quality of anaesthetic induction, as graded by the anaesthetist, was similar in the four techniques. Apnoea was more frequent with the propofol infusion method than the other three methods of anaesthesia. There was no significant difference in the incidence of other respiratory side effects. Involuntary movements were noted in the patients having intravenous agents. These were more frequent with propofol than

with thiopentone . Arrhythmias were seen in patients receiving thiopentone and halothane but none were seen in those who had had propofol for anaesthesia. However, none of these complications was serious enough to interfere with the progress of surgery. The higher incidence of respiratory complications in the propofol infusion anaesthesia was probably due to the difficulty in maintaining an optimum level of anaesthesia with a new technique of anaesthesia.

Recovery

Recovery characteristics were assessed in the same 163 patients, based on the time from the end of anaesthesia to (1) achieve a full Steward score which included three categories of assessment: level of consciousness, airway control, and movement, (2) open eyes on command, and (3) orientation to name and answering simple questions such as age. Psychomotor performance was also included in the assessment to compare the recovery of co-ordination ability. Recovery was slowest with propofol infusion. However, children who had propofol anaesthesia (bolus as well as infusion) felt less giddy than those children who had had thiopentone and halothane anaesthesia, and they had less postoperative vomiting. The recovery profiles were similar in the three techniques using propofol bolus or thiopentone or halothane for induction and halothane maintenance.

Modification of the total intravenous anaesthetic technique, such as using supplementary opioids to suppress the response to noxious stimulation, and further evaluation is needed before the place of propofol infusion in paediatric anaesthesia can be determined.

CHAPTER 10

Conclusions

CONCLUSIONS

Induction

Propofol, in doses of 2.5 to 3.5 $mg.kg^{-1}$, is a satisfactory agent for induction of anaesthesia in unpremedicated children. Younger children need more than older children within this dose range.

Induction of anaesthesia using propofol causes more cardiovascular depression than after an equipotent dose of thiopentone. Arterial pressure is reduced by 30%, and is associated with a reduction in cardiac index and systemic vascular resistance. Compensation by the baroreflex appears to be impaired more in children less than two years old. This degree of cardiovascular depression is well tolerated in healthy children, but potentially harmful in those with a compromised cardiovascular function.

The pharmacokinetic variables after a single dose (2.5 $mg.kg^{-1}$) of propofol have a good correlation with body weight, but not with the age of the patients after the pharmacokinetic variables were adjusted for the body weight. There was no difference in protein binding of propofol between younger and older children. These imply that the difference in the dose required for induction of anaesthesia in different age groups of children is not due to pharmacokinetic differences, although differences in pharmacodynamics cannot be excluded.

Maintenance

Pharmacokinetic-model-controlled infusion of propofol for maintenance of anaesthesia is easy and reliable to use in children provided that the pharmacokinetic parameters are accurate. A revised version was developed from a published model. The precision was 21.5% and the bias -0.1%.

Compared with thiopentone and halothane, propofol anaesthesia was associated with more pain on injection, involuntary movements, respiratory side effects, but fewer arrthymias during the procedure.

Recovery

Recovery following anaesthesia using propofol infusion was slower than that following propofol given as bolus dose and maintenance with halothane. Similarly, it was slower than that after thiopentone or halothane induction and maintenance with halothane. Differences between the latter three techniques were not significant. Propofol anaesthesia was associated with less vomiting and giddiness after the operation.

Conclusion

This thesis evaluated the use of propofol for anaesthesia in children undergoing short surgical procedures. It upheld the hypothesis that propofol is an effective induction agent in paediatric anaesthesia. However, the place of propofol infusion for maintenance needs further modification and evaluation before it can be accepted as an alternative to existing techniques. As this agent is still relatively new at this stage, it should be used with care. Any adverse reactions should be reported to the local Committee on the Safety of Medicines for data collection.

SECTION VII
REFERENCES

REFERENCES

Adam HK, Briggs LP, Bahar M, Douglas EJ, Dundee JW. Pharmacokinetic evaluation of ICI 35 868 in man, Single induction doses with different rates of injection. *British Journal of Anaesthesia* 1983; **55**: 97-102.

Adinolfi M, Beck SE, Haddad SA, Seller MJ. Permeability of the blood-cerebrospinal fluid barrier to plasma proteins during foetal and perinatal life. *Nature* 1976; **259:** 140-141.

Albanese J, Martin C, Lacarelle B, Saux P, Durand A, Gouin F. Pharmacokinetics of long term propofol infusion used for sedation in ICU patients. *Anesthesiology* 1990; **73:** 214-217.

Alverson DC, Eldridge M, Dillon T, Yabek SM, Berman W. Noninvasive pulsed Doppler determination of cardiac output in neonates and children. *The Journal of Pediatrics* 1982; **101**: 46-50.

Andreev A, Rouby JJ, Léger P, Devilliers C, Durand F, Poete P, Cabrol C, Viars P. Peripheral vascular effects of propofol. *Anesthesiology* 1988; **69**: A567

Annotation. Paediatric anaesthesia. *British Medical Journal* 1978; **2**: 717.

Aranda JV, MacLeod SM, Renton KW, Eade NR Hepatic microsomal drug oxidation and electron transport in newborn infants. *The Journal of Pediatrics* 1974; **85**: 534-542.

Aun CST, Short SM, Leung DHY, Oh TE. Induction dose-response of propofol in unpremedicated children. *British Journal of Anaesthesia* 1992; **68** : 64 - 67

Aun CST, Sung RYT, O'Meara ME, Short TG, Oh TE. Cardiovascular effects of iv induction in children: comparison between propofol and thiopentone. *British Journal of Anaesthesia* 1993; **70** : 647 - 653.

Aun CST, Short TG, O'Meara ME, Leung DHY, Oh TE. Recovery after propofol infusion anaesthesia in children: comparison with propofol. thiopentone or halothane induction followed by halothane maintenance. *British Journal of Anaesthesia* 1994; **72:** 554-558.

Bakhle YS. Pharmacokinetic and metabolic properties of lung. *British Journal of Anaesthesia* 1990; **65**: 79-93.

Besunder JB, Reed MD, Blumer JL. Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part I). *Clinical Pharmacokinetics* 1988a; **14**: 189-216.

Besunder JB, Reed MD, Blumer JL. Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part II). *Clinical Pharmacokinetics* 1988b; **14**: 261-286.

Bevan JC. Propofol-related convulsions. *Canadian Journal of Anaesthesia* 1993; **40**: 805-809.

Bloomfield EL, Masaryk TJ, Caplin A, Schubert A, Hayden J, Goske MJ. Pediatric sedation for MRI of the brain and spine : a comparative study of pentobarbital vs propofol. *Anesthesia and Analgesia* 1993;**76**: S22.

Booker P. Intravenous agents in paediatric anaesthesia In: Sumner E, Hatch DJ, eds.*Textbook of Paediatric Anaesthetic Practice.* London, Bailliere Tindall; 1989; 61-90

Boréus LO, Jalling B, Källberg N. Phenobarbital metabolism in adults and in newborn infants. *Acta Paediatrica Scandinavica* 1978; **67**: 193-200.

Boréus LO. Distribution. In: Boréus LO, ed. *Principles of Pediatric Pharmacology*. New York, Churchill Livingstone; 1982a; 46-74.

BoréusLO. Biotransformation. In: Boréus LO, ed. *Principles of Pediatric Pharmacology*. New York, Churchill Livingstone; 1982b; 91-114.

Boréus LO. Renal excretion. In: Boréus LO, ed. *Principles of Pediatric Pharmacology*. New York, Churchill Livingstone; 1982c; 115-134.

Borgeat A, Popovic V, Meier D, Schwander D. Comparison of propofol and thiopentone/halothane for short duration ENT surgical procedures in children. *Anesthesia and Analgesia* 1990; **71**: 511-515.

Borgeat A, Dessibourg C, Popovic V, Meier D, Blanchard M, Schwander D. Propofol and spontaneous movements: An EEG study. *Anesthesiology* 1991; **74**: 24-27.

Borgeat A, Fuchs T, Wilder-Smith O, Tassonyi E. The effect of nalbuphine and droperidol on spontaneous movements during induction of anesthesia with propofol in children. *Journal of Clinical Anesthesia* 1993; **5**: 12- 15.

Briggs LP, Clarke RSJ, Dundee JW, Moore J, Bahar M, Wright PJ. Use of di-isopropyl phenol as main agent for short procedures. *British Journal of Anaesthesia* 1981; 53: 1197-1202.

Briggs LP, White M. The effects of premedication on anaesthesia with propofol (Diprivan). *Postgraduate Medical Journal* 1985; 61: Suppl 3: 35-37.

Bristow JD, Prys - Roberts C, Fisher A, Pickering TG, Sleight P. Effects of anesthesia on baroreflex control of heart rate in man. *Anesthesiology* 1969; **31**: 422- 428

Brook CGD. Determination of body composition of children from skinfold measurements. *Archives of Disease in Childhood* 1971; **46**: 182-184.

Brooker J, Hull CJ, Stafford M. Effect of lognocaine on pain caused by propofol injection. *Anaesthesia* 1985; **40**: 91-92.

Brooker J, Redfern N. Pain on injection with propofol. *Anaesthesia* 1986; **41**: 1062.

Brown TCK. Anaesthetic management. In: Brown TCK, Fisk GC, eds *Anaesthesia for Children.* 2nd ed. Oxford, Blackwell Scientific Publications; 1992; 103-126.

Browne BL, Wolf AR, Prys-Roberts C. Dose requirements for propofol in children during total iv anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 396p.

Browne BL, Prys-Roberts C, Wolf AR. Propofol and alfentanil in children: Infusion technique and dose requirement for total iv anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 570-576.

Burch PG, Stanski DR. The role of metabolism and protein binding in thiopental anesthesia. *Anesthesiology* 1983; **58**: 146-152.

Calafiore P, Stewart WJ. Doppler echocardiographic quantitation of volumetric flow rate. *Cardiology Clinics* 1990; **8:** 191- 202

Cameron E, Johnston G, Crofts S, Morton NS. The minimum effective dose of lignocaine to prevent injection pain due to propofol in children. *Anaesthesia* 1992; **47**: 604-606.

Campbell GA, Morgan DJ, Kumar K, Crankshaw DP. Extended blood collection period required to define distribution and elimination kinetics of propofol. *British Journal of Clinical Pharmacology* 1988; **26**: 187-190.

Cannon DJ. Instrumentation and techniques for therapeutic drug monitoring. *Clinics in Laboratory Medicine* 1987; **7**: 325-334.

Chan K, Gin T. Liquid chromatographic assay for propofol, a new i.v. anaesthetic, in maternal and umbilical blood samples. *Neuroscience Letters* 1990; **37**(suppl): S23

Choonara I, Ekbom Y, Lindstrom B, Rane A. Morphine sulphation in children. *British Journal of Clinical Pharmacology* 1990; **30**: 897-900.

Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol . *British Journal of Anaesthesia* 1988; **60**: 3-9.

Clarke RSJ, Dundee JW, Garrett RT, McArdle GK, Sutton JA. Adverse reactions to intravenous anaesthetics. A survey of 100 reports. *British Journal of Anaesthesia* 1975; **47**: 575-585.

Clayton DG, Webb RK, Ralston AC, Duthie D, Runciman WB. A comparison of the performance of 20 pulse oximeters under conditions of poor perfusion. *Anaesthesia* 1991; **46**: 3-10.

Coates DP, Monk CR, Prys-Roberts C, Turtle M. Hemodynamic effects of infusions of the emulsion formulation of propofol during nitrous oxide anesthesia in humans. *Anesthesia and Analgesia* 1987; **66**: 64-70.

Cockshott ID. Propofol (Diprivan) pharmacokinetics and metabolism - an overview. *Postgraduate Medical Journal* 1985; **61** (Suppl 3); 45-50.

Cockshott ID, Briggs LP, Douglas EJ, White M. Pharmacokinetics of propofol in female patients. Studies using single bolus injections. *British Journal of Anaesthesia* 1987a; **59**: 1103-1110.

Cockshott ID, Douglas EJ, Prys Roberts C, Turtle M, Coates DP. Pharmacokinetics of propofol during and after i.v. infusion in man *British Journal of Anaesthesia* 1987b; **59**: 941P-942P.

Cockshott ID, Douglas EJ, Prys-Roberts C, Turtle M, Coates DP. The pharmacokinetics of propofol during and after intravenous infusion in man. *European Journal of Anaesthesiology* 1990; **7**: 265-275.

Cockshott ID, Haywood J. Extended Least Squares Curve Fitting: A Comparison of SIPHAR and MKMODEL. *Biopharmaceutics and Drug Disposition* 1992; **13**: 461-480

Coley S, Mobley KA, Bone ME, Fell D. Haemodynamic changes after induction of anaesthesia and tracheal intubation following propofol or thiopentone in patients of ASA grade I and III. *British Journal of Anaesthesia* 1989; **63**: 423-428.

Collins GGS. Effects of the anaesthetic 2,6-diisopropyl-phenol on synaptic transmission in the rat olfactory cortex slice. *British Journal of Pharmacology* 1988; 95: 939-949.

Committee on Safety of Medicines. Propofol. Current Problems 20. no 5, 1987.

Committee on Safety of Medicines. Propofol. Current Problems 26. no 3, 1989.

Concas A, Santoro G, Serra M, Sanna E, Biggio G. Neurochemical action of the general anaesthetic propofol on the chloride ion channel coupled with $GABA_A$ receptors. *Brain Research* 1991; **542**: 225-232.

Conway CM, Ellis DB. The haemodynamic effects of short acting barbiturates. *British Journal of Anaesthesia* 1969; **41**: 534-542

Cook DR, Davies PJ. Pharmacology of pediatric anesthesia. In: Motoyama EK, Davies PJ, eds *Smith's Anesthesia for Infants and Children*. 5th ed. St. Louis, CV Mosby; 1990; 157-197.

Coté CJ, Goudsouzian NG, Liu LMP, Dedrick DF, Rosow CE. The dose response of intravenous thiopental for the induction of general anesthesia in unpremediacted children. *Anesthesiology* 1981; **55:** 703-705.

Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effect of propofol anesthesia on baroreflex activity in humans. *Anesthesia and Analgesia*1987; **66**: 1115-1120.

Cummings GC, Dixon J, Kay NH, Windsor JPW, Major E, Morgan M, Sear JW, Spence AA, Stephenson DK. Dose requirements of ICI 35,868 (Propofol, 'Diprivan') in a new formulation for induction of anaesthesia. *Anaesthesia* 1984; **39**: 1168-1171.

Deer TR, Rich GF. Propofol tolerance in a pediatric patient. *Anesthesiology* 1992; **77**: 828-829.

Documenta Geigy, In *Ciba-Geigy* 7th ed. Basle, 1970; 538

Doyle E, McFadzean W, Morton NS. I.V. Anaesthesia with propofol using a target-controlled infusion system: comparison with inhalational anaesthesia for general surgical procedures in children. *British Journal of Anaesthesia* 1993; **70**: 542-545.

Doze VA, Westphal LM, White PF. Comparison of propofol with methohexital for outpatient anesthesia. *Anesthesia and Analgesia* 1986; **65**: 1189-1195.

Duncan PG, Gregory GA, Wade JG. The effect of nitrous oxide on baroreceptor function in newborn and adult rabbits. *Canadian Anaesthetists' Society Journal* 1981; **28**: 339-341.

Durnin JVGA, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. *British Journal of Nutrition* 1967; **21**: 681-689.

Dwyer R, McCaughey W, Lavery J, McCarthy G, Dundee JW. Comparison of propofol and methohexitone as anaesthetic agents for electroconvulsive therapy. *Anaesthesia* 1988; **43**: 459-462.

Ebert TJ. Differential effects of nitrous oxide on baroreflex control of heart rate and peripheral sympathetic nerve activity in humans. *Anesthesiology* 1990; **72**: 16-22.

Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP. Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. *Anesthesiology* 1992; **76**: 725-733.

Eckstein JW, Hamilton WK, McCammond JM. The effect of thiopental on peripheral venous tone. *Anesthesiology* 1961; **22**: 525-528

Elder JD, Nagano SM, Eastwood DW, Harnagel D. Circulatory changes associated with thiopental anesthesia in man. *Anesthesiology* 1955; **16**: 394-400.

Etsten B, Li TH. Hemodynamic changes during thiopental anesthesia in humans: cardiac output, stroke volume, total peripheral resistance and intrathoracic blood volume. *Journal of Clinical Investigation* 1955; **34**: 500-510.

Evans JM, Keogh JAM. Adverse reactions to intravenous anaesthetic induction agents. *British Medical Journal* 1977; **2**: 735-736.

Fahmy NR, Durkin TA, Caliguri EJ, Mefford I. Circulatory and catecholamine responses to endotracheal intubation after induction with thiopental or propofol. *Anesthesiology* 1989; **71**: A946.

Fahy LT, van Mourik GA, Utting JE. A comparison of the induction characteristics of thiopentone and propofol (2,6-di-isopropyl phenol). *Anaesthesia* 1985; **40**: 939-944.

Fairfield JE, Dritsas A, Beale RJ. Haemodynamic effects of propofol: Induction with 2.5mg. kg^{-1}. *British Journal of Anaesthesia* 1991; **67**: 618-620.

Fell D, Gough MB, Northan AA, Henderson CU. Diazepam premedication in children, plasma levels and clinical effects. *Anaesthesia* 1985; **40**: 12-17.

Finley GA, MacManus B, Sampson SE, Fernandez CV, Retallick R. Delayed seizures following sedation with propofol. *Canadian Journal of Anaesthesia* 1993; **40**: 863-865.

Finney DJ. *Probit Analysis.* 2nd ed. Cambridge, Cambridge University Press; 1971.

Flickinger H, Fraimow W, Cathcart RT, Nealon TF. Effect of thiopental induction on cardiac output in man. *Anesthesia and Analgesia* 1961; **40:** 693-700.

Friesen RH, Lichtor JL. Indirect measurement of blood pressure in neonates and infants utilizing an automatic noninvasive oscillometric monitor. *Anesthesia and Analgesia* 1981; **60**: 742-745.

Friis-Hansen B. Body water compartments in children: Changes during growth and related changes in body composition. *Pediatrics*. 1961; **28**: 169-181.

Friis-Hansen B. Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth. *Pediatrics* 1971; **47**: 264-274.

Gauss A, Heinrich H, Wilder-Smith OHG. Echocardiographic assessment of the haemodynamic effects of propofol: a comparison with etomidate and thiopentone. *Anaesthesia* 1991; **46**: 99-105.

Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as a constant rate intravenous infusion in humans. *Anesthesia and Analgesia* 1987; **66**: 1256-1263.

Gepts E, Camu F. Pharmacokinetics of intravenous induction agents. In: White PF, ed. Kinetics of Anaesthetic Drugs in Clinical Anaesthesiology. *Clinical Anaesthesiology*. London, Bailliere Tindall; 1991; **5**: (3) 513-542.

Gibaldi M, Perrier D. Multicompartment models. In: Swarbrick J, ed. *Pharmacokinetics. Drugs and the Pharmaceutical Sciences.* New York : Marcel Dekker; 1982; 15: 45-111.

Gilman JT. Therapeutic drug monitoring in the neonate and paediatric age group. Problems and clinical pharmacokinetic implications. *Clinical Pharmacokinetics* 1990; 19: 1-10.

Gin T, Gregory MA, Chan K, Buckley T, Oh TE. Pharmacokinetics of propofol in women undergoing elective Caesarian section. *British Journal of Anaethesia* 1990, **64**: 148-153.

Gin T, Yau G, Chan K, Gregory MA, Oh TE. Disposition of propofol infusions for Caesarean section. *Canadian Journal of Anaesthesia* 1991; **38**: 1: 31-36.

Gin T, O'Meara ME, Kan AF, Leung RKW, Tan P, Yau G. Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at Caesarean section. *British Journal of Anaesthesia* 1993; **70**: 311-316.

Glen JB, Davies GE, Thomson DS, Scarth SC, Thompson AV. An animal model for the investigation of adverse responses to IV anaesthetic agents and their solvents. *British Journal of Anaesthesia* 1979; **51**: 819-827.

Glen JB, Hunter SC. Pharmacology of an emulsion formulation of ICI 35 868. *British Journal of Anaesthesia* 1984; **56**: 617- 625.

Gold MI, Abraham EC, Herrington C. A controlled investigation of propofol, thiopentone and methohexitone. *Canadian Journal of Anaesthesia* 1987; **34**: 478-483.

Goodman NW, Black AMS, Carter JA. Some ventilatory effects of propofol as sole anaesthetic agent. *British Journal of Anaesthesia* 1987; **59:** 1497-1503.

Gregory GA. The baroresponses of preterm infants during halothane anaesthesia *Canadian Anaesthesia Society Journal* 1982; **29**: 105-107.

Gregory MA, Gin T, Yau G, Leung RKW, Chan K, Oh TE. Propofol infusion anaesthesia for Caesarean section. *Canadian Journal of Anaesthesia* 1990; **37**: 514-520.

Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction, comparison of the effects of thiopentone and propofol. *Anaesthesia* 1985; **40**: 735-740.

Grounds RM, Moore M, Morgan M. The relative potencies of thiopentone and propofol. *European Journal of Anaesthesiology* 1986; **3:** 11-17.

Grounds RM, Maxwell DL, Taylor MB, Aber V, Royston D. Acute ventilatory changes during I.V. induction of anaesthesia with thiopentone or propofol in man. Studies using inductance plethysmography. *British Journal of Anaesthesia* 1987; **59**: 1098-1102.

Hannallah RS, Baker SB, Casey W, McGill WA, Broadman LM, Norden JM. Propofol: Effective dose and induction characteristics in unpremedicated children. *Anaesthesiology* 1991; **74** : 217-219

Hannallah RS, Britton JT, Schafer PG, Patel RI, Norden JM. Propofol anaesthesia in paediatric ambulatory patients: a comparison with thiopentone and halothane. *Canadian Journal of Anaesthesia* 1994; **41**: 12-18.

Hara M, Kai Y, Ikemoto Y. Propofol activates $GABA_A$ receptor-chloride ionophore complex in dissociated hippocampal pyramidal neurons of the rat. *Anesthesiology* 1993; **79:** 781-788.

Hatch DJ. Anaesthesia for children. Editorial. *Anaesthesia* 1984; **39**: 405-406.

Hatch DJ, Sumner E. Perinatal physiology. In: *Neonatal Anaesthesia and Perioperative Care.* 2nd ed. London, Edward Arnold; 1986; 1-53.

Heath PJ, Kennedy DJ, Ogg TW, Dunling C, Gilks WR. Which intravenous induction agent for day surgery? A comparison of propofol, thiopentone, methohexitone and etomidate. *Anaesthesia* 1988; **43**: 365-368.

Hook JB, Hewitt WR. Development of mechanisms for drug excretion. *The American Journal of Medicine* 1977; **62**: 497-506.

Hull CJ. Variation in drug disposition I: The influence of age, sex and heredity . In *Pharmacokinetics for Anaesthesia* Oxford, Butterworth; 1991; 111-125.

James R, Glen JB. Synthesis, biological evaluation and preliminary structure-activity considerations of a series of alkylphenols as intravenous anaesthetic agents. *Journal of Medical Chemistry* 1980; **23**: 1350-1357.

Jones RDM, Chan K, Andrew LJ. Pharmacokinetics of propofol in children. *British Journal of Anaesthesia* 1990; **65** : 661 - 667

Jonmarker C, Westrin P, Larsson S, Werner O. Thiopental requirements for induction of anesthesia in children. *Anesthesiology* 1987; **67**: 104-107.

Juchau MR, Pedersen MG. Drug biotransformation reactions in the human fetal adrenal gland. *Life Science II* 1973; **12**: 193-204.

Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clinical Pharmacokinetics* 1989; **17**: (5) 308-326.

Kaplan JA. Hemodynamic monitoring. In: Kaplan JA, ed. *Cardiac Anesthesia.* 2nd ed. Philadelphia, WB Saunders; 1987; 179-225.

Kataria B, Dubois M, Chen G, Balter N, Schwartz S, Lea D. Pharmacokinetics of single dose propofol in children. *Anesthesia and Analgesia* 1992; **74**: S160.

Kataria BK, Ved SA, Nicodemus HF, Hoy GR, Lea D, Dubois MY, Mandema JW, Shafer SL. The pharmacokinetics of propofol in children using three different data analysis approaches. *Anesthesiology* 1994; **80:** 104-122.

Kawar P, Briggs LP, Bahar M, McIlroy PDA, Dundee JW, Merrett JD, Nesbitt GS. Liver enzyme studies with disoprofol (ICI 35,868) and midazolam. *Anaesthesia* 1982; **37**: 305-308.

Kay B, Rolly G. ICI 35868, a new intravenous induction agent. *Acta Anaesthesiologica Belgica* 1977; **28**: 303-316

Kay NH, Sear JW, Uppinton J, Cockshott ID, Douglas EJ. Disposition of propofol in patients undergoing surgery. A comparison in men and women. *British Journal of Anaesthesia* 1986; **58** : 1075-1079.

Kearns GL, Reed MD. Clinical Pharmacokinetics in infants and children. A reappraisal. *Clinical Pharmacokinetics* 1989; 17(suppl.1): 29-67.

Kingston HGG, Kendrick A, Sommer KM, Olsen GD, Downes H. Binding of thiopental in neonatal serum. *Anesthesiology* 1990; **72**: 428-431.

Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS. Pharmacokinetics of propofol (Diprivan) in elderly patients. *British Journal of Anaesthesia* 1988; **60**: 146 - 150.

Korttila K, Linnoila M, Ertama P, Häkkinen S, Eng D. Recovery and simulated driving after intravenous anesthesia with thiopental, methohexital, propanidid, or alphadione. *Anesthesiology* 1975; **43**: 291-299.

Kosarussavadi B. Premedication. In: Bell C, Hugues CW, Oh TH, eds. *The Pediatric Anesthesia Handbook.* St. Louis, Mosby Year Book; 1991; 71-80.

Kupferberg HJ, Way EL. Pharmacologic basis for the increased sensitivity of the newborn rat to morphine. *Journal of Pharmacology and Experimental Therapeutics* 1963; **141**: 105-112.

Kurz H, Michels H, Stickel HH. Differences in the binding of drugs to plasma proteins from newborn and adult man. II. *European Journal of Clinical Pharmacology* 1977; **11**: 469-472.

Larsson S, Asgeirsson B, Magnusson J. Propofol-fentanyl anesthesia compared to thiopental-halothane with special reference to recovery and vomiting after pediatric strabismus surgery. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 182-186.

Lau SP, Fung KP, Leung SSF, Lam YM, Davies DP. Height, weight and head circumference reference standards for southern Chinese, Hong Kong born children aged 3-18 years. *Hong Kong Journal of Paediatrics* 1987; **4**: 104-118.

Laxenaire M-C, Gueant J-L, Bermejo E, Mouton C, Navez MT. Anaphylactic shock due to propofol. *Lancet* 1988; **ii**: 739-740.

Laxenaire M-C, Mata-Bermejo E, Moneret-Vautrin DA, Gueant J-L. Life threatening anaphylactoid reactions to propofol (Diprivan). *Anesthesiology* 1992; **77**: 275-280.

Laycock GJA. Opisthotonos and propofol: a possible association. *Anaesthesia* 1988; **43**: 257.

Laycock GJA, Mitchell IM, Morton NS, Logan RW. EEG burst suppression and haemodynamic effects with propofol during cardiopulmonary bypass in children. Canadian Journal of Anaesthesia 1991a; **38**: A 140.

Laycock GJA, Mitchell IM, Morton NS, Logan RW, Black J. Metabolic and endocrine effects of propofol during cardiopulmonary bypass in children. Canadian Journal of Anaesthesia 1991a; **38**: A 169.

Laycock GJA, Mitchell IM, Paton RD, O'B. Donaghey SF, Logan RW, Morton NS. EEG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects. *British Journal of Anaesthesia* 1992; **69**: 356-362.

Lees NW, McCulloch M, Mair WB. Propofol ('Diprivan') for induction and maintenance of anaesthesia. *Postgraduate Medical Journal* 1985; **61**: (suppl 3) 88-89.

Leithe ME, Hermiller JB, Magorien RD, Unverferth DV, Leier CV. The effect of age on central and regional hemodynamics. *Geronotology* 1984; **30**:240-246.

Leslie K, Crankshaw DP. Potency of propofol for loss of consciousness after a single dose. *British Journal of Anaesthesia* 1990; **64**: 734-736.

Leung SSF, Lui S, Lo L, Lam YM, Davies DP. Growth standards for weight, length and head circumference: Hong Kong infants Birth - 2 years. *Hong Kong Journal of paediatrics* 1988; **5**: 109-124.

Lippmann M, Paicius RM, Gingerich S, Owens R, Mok MS, Appel P. A controlled study of the hemodynamic effects of propofol versus thiopentone during anesthesia induction. *Seminars in Anesthesia* 1988; **7**: No 1: (Suppl 1): 116-122.

Lippmann M, Boer F, Ros P, Bovill JG, Brummelen PV, Van Der Krogt J. Propofol: Effect on the myocardium compared with the peripheral vascular system. *British Journal of Anaesthesia* 1991; **66**: 416-417.

Logan MR, Duggan JE, Levack ID, Spence AA. Single-shot iv anaesthesia for outpatient dental surgery. Comparison of 2,6 Di-isopropyl phenol and methohexitone. *British Journal of Anaesthesia* 1987; **59**: 179-183.

Lundy JS. Intravenous anesthesia : Preliminary report of the use of two new thiobarbiturates. *Proceedings of Staff Meetings of the Mayo Clinic* 1935; **10**: 536- 543

MacKenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. *British Journal of Anaesthesia* 1985a; **57**: 725-731.

MacKenzie N, Grant IS. Comparison of propofol with methohexitone in the provision of anaesthesia for surgery under regional blockade. *British Journal of Anaesthesia* 1985b; **57**: 1167-1172.

Maitre PO, Shafer SL. A simple pocket calculator approach to predict anesthetic drug concentrations from pharmacokinetic data. *Anesthesiology* 1990; **73**: 332-336.

Major E, Verniquet AJW, Waddell TK, Savege TM, Hoffler DE, Aveling W. A study of three doses of ICI 35868 for induction and maintenance of anaesthesia. *British Journal of Anaesthesia* 1981; **53:** 267-272.

Manschot HJ, Meursing AE, Axt P, Byttebier GO, Erdmann W. Propofol requirements for induction of anesthesia in children of different age groups. *Anesthesia and Analgesia* 1992; **75**: 876-879.

Marsh B, White M, Morton N, Kenny GNC. Pharmacokinetic model driven infusion of propofol in children.*British Journal of Anaesthesia* 1991, **67**: 41-48.

Martin TM, Nicolson SC, Bargas MS. Propofol anesthesia reduces emesis and airway obstruction in pediatric outpatients. *Anesthesia and Analgesia* 1993; **76**: 144-148.

McCollum JSC, Dundee JW. Comparison of induction characteristics of four intravenous anaesthetic agents. *Anaesthesia* 1986; **41**: 995-1000.

McCollum JSC, Milligan KR, Dundee JW. The antiemetic action of propofol. *Anaesthesia* 1988; **43**: 239-240.

McCulloch MJ, Lees NW. Assessment and modification of pain on induction with propofol (Diprivan) *Anaesthesia* 1985; **40:** 1117-1120.

McHale SP, Konieczko K. Anaphylactoid reaction to propofol anaesthesia. *Anaesthesia* 1992; **47**: 864-865.

McKeating K, Bali IM, Dundee JW. The effects of thiopentone and propofol on upper airway integrity. *Anaesthesia* 1988; **43**: 638-640.

McLeskey CH, Walawander CA, Nahrwold ML, Roizen MF, Stanley TH, Thisted RA, White PF, Apfelbaum JL, Grasela TH, Hug CC Jr. Adverse events in a multicenter phase IV study of propofol: Evaluation by anesthesiologists and postanesthesia care unit nurses. *Anesthesia and Analgesia* 1993; **77**: S3-S9.

Mellander M, Sabel K-G, Caidahl K, Solymar L, Eriksson B. Doppler determination of cardiac output in infants and children: Comparison with simultaneous thermodilution. *Pediatric Cardiology* 1987; **8**: 241-246.

Mettau JW, Degenhart HJ, Visser HKA, Holland WPS. Measurement of total body fat in newborns and infants by absorption and desorption of nonradioactive xenon. *Pediatric Research* 1977; **11**: 1097-1101.

Mirakhur RK. Induction characteristics of propofol in children: comparison with thiopentone. *Anaesthesia* 1988; **43**: 593-598.

Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina K. Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. Studies in association with peripheral arterial surgery. *British Journal of Anaesthesia* 1987; 59: 954-960.

Morris P. Paediatric day-case surgery.*British Journal of Anaesthesia* 1992; **68**: 3-4.

Morselli PL, Franco-Morselli R, Bossi L. Clinical pharmacokinetics in newborns and infants, age related differences and therapeutic implications. *Clinical pharmacokinetics* 1980; **5**: 485-527.

Morton NS, Wee M, Christie G, Gray IG, Grant IS. Propofol for induction of anaesthesia in children. A comparison with thiopentone and halothane inhalational induction. *Anaesthesia* 1988; **43**: 350-355.

Morton NS. Abolition of injection pain due to propofol in children. *Anaesthesia* 1990; **45**: 70.

Morton NS, Johnston G, White M, Marsh BJ. Propofol in paediatric anaesthesia. *Paediatric Anaesthesia* 1992; **2:** 89-97.

O'Toole DP, Milligan KR, Howe JP, McCollum JSC, Dundee JW. A comparison of propofol and methohexitone as induction agents for day case isoflurane anaesthesia. *Anaesthesia* 1987; **42**: 373-376.

Olkkola KT, Maunuksela E-L, Korpela R. Pharmacokinetics of intravenous buprenorphine in children. *British Journal of Clinical Pharmacology* 1989; **28:** 202-204.

Olsen RW, Tobin AJ. Molecular biology of $GABA_A$ receptors. *Federation of American Societies for Experimental Biology Journal* 1990; **4:** 1469-1480.

Onishi S, Yoshiho O, Nishimura Y, Itoh S, Isobe K, Hosoe A, Yamamoto T, Yamamoto T. Distribution of phenobarbital in serum brain and other organs from pediatric patients. *Development Pharmacology and Therapeutics* 1984; **7**: 153-159.

Paech MJ, Storey JM. Propofol and seizures. *Anaesthesia and Intensive Care* 1990; **18**: 585.

Painter MJ, Pippenger C, Wasterlain C, Barmada M, Pitlick W, Carter G, Abern S. Phenobarbital and phenytoin in neonatal seizures: metabolism and tissue distribution. *Neurology* 1981; **31**: 1107-1112.

Park MK, Menard SM. Accuracy of blood pressure measurement by the Dinamap monitor in infants and children. *Pediatrics* 1987; **79**: 907-914.

Parke TJ, Stevens JE, Rice ASC, Greenaway CL, Bray RJ, Smith PJ, Waldmann CS, Verghese C. Metabolic acidosis and fatal myocardial failure after propofol infusion in children, five case reports. *British Medical Journal* 1992; **305**; 613-616.

Patel DK, Keeling PA, Newman GB, Radford P. Induction dose of propofol in children. *Anaesthesia* 1988; **43:** 949-952

Plummer GF. Improved method for the determination of propofol in blood by high performance liquid chromatography with fluorescence detection. *Journal of Chromatography* 1987; **421**: 171 - 176

Purcell-Jones G, James IG. The characteristics of propofol ('Diprivan') for induction of general anaesthesia for paediatric surgery (Abstract). *Postgraduate Medical Journal* 1985; **61**: (Suppl 3) 115.

Purcell-Jones G, Yates A, Baker JR, James IG. Comparison of the induction characteristics of thiopentone and propofol in children *British Journal of Anaesthesia* 1987; **59**: 1431-1436.

Puttick N, Rosen M. Propofol induction and maintenance with nitrous oxide in paediatric outpatient dental anaesthesia. A comparison with thiopentone -nitrous oxide- halothane. *Anaesthesia* 1988; **43**: 646-649.

Radde IC. Drugs and protein binding. In: Radde IC, MacLeod SM, eds. *Pediatric Pharmacology and Therapeutics* 2nd ed. St. Louis, Mosby; 1993a; 31-42.

Radde IC. Growth and drug distribution. In: Radde IC, MacLeod SM, eds. *Pediatric Pharmacology and Therapeutics* 2nd ed. St. Louis, Mosby; 1993b; 43-56.

Radde IC. Renal function and elimination of drugs during development. In: Radde IC, MacLeod SM, eds. *Pediatric Pharmacology and Therapeutics* 2nd ed. St. Louis, Mosby; 1993c; 87-110.

Radde IC, MacLeod SM. Therapeutic and nontherapeutic research in children. In: Radde IC, MacLeod SM, eds. *Pediatric Pharmacology and Therapeutics* 2nd ed. St. Louis, Mosby; 1993d; 604-611.

Redfern N, Stafford MA, Hull CJ. Incremental propofol for short procedures. *British Journal of Anaesthesia* 1985; **57** : 1178 -1182.

Rein AJJ, Hsieh KS, Elixson M, Colan SD, Lang P, Sanders SP, Castaneda AR. Cardiac output estimates in the pediatric intensive care unit using a continuous-wave Doppler computer: validation and limitations of the technique. *American Heart Journal* 1986; **112**: 97-103.

Riou B, Besse S, Lecarpentier Y, Viars P. In vitro effects of propofol on rat myocardium. *Anesthesiology* 1992; **76**: 609-616.

Roberts FL, Dixon J, Lewis GTR, Tackley RM, Prys-Roberts C. Induction and maintenance of propofol anaesthesia. A manual infusion scheme. *Anaesthesia* 1988; **43:** 14-17.

Robinson S. Cardiovascular Physiology in Pediatrics. In: Gregory GA, ed. *Pediatric Anesthesia.* New York, Churchill Livingstone; 1983; 9-33.

Roure P, Jean N, Leclerc A-C, Cabanel N, Levron J-C, Duvaldestin P. Pharmacokinetics of alfentanil in children undergoing surgery. *British Journal of Anaesthesia* 1987; **59** : 1437-1440.

Runcie CJ, Mackenzie SJ, Arthur DS, Morton NS. Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone. *British Journal of Anaesthesia* 1993; **70**: 192-195.

Saarnivaara L, Hiller A, Oikkonen M. QT interval, heart rate and arterial pressures using propofol, thiopentone or methohexitone for induction of anaesthesia in children. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 419-423.

Saint-Maurice C, Cockshott ID, Douglas EJ, Richard MO, Harmey JL. Pharmacokinetics of propofol in young children after a single dose. *British Journal of Anaesthesia* 1989; **63** : 667-670.

Salonen MA, Maze M. Molecular mechanism of action for hypnotic and sedative agents. In: Feldman S, Scurr CF, Paton W, eds. *Mechanisms of Drugs in Anaesthesia.* 2nd ed. London, Edward Arnold; 1993; 201-210.

Saunders NR. Ontogeny of the blood brain barrier. *Experimental Eye Research* 1977, Suppl., 523-550.

Saunders PRI, Harris MNE. Opisthotonus and other unusual neurological sequelae after outpatient anaesthesia. *Anaesthesia* 1990; **45**: 552-557.

Savege TM. New anaesthetic drugs and techniques-enflurane, etomidate and total intravenous anaesthesia. In: Langton Hewer C, Atkinson RS, eds. *Recent Advances in Anaesthesia and Analgesia* Edinburgh, Churchill Livingstone; 1979; 13: 1-22.

Schieber RA. Cardiovascular physiology in infants and children. In: Motoyama EK, Davis PJ, eds. *Smith's Anesthesia for Infants and Children.* St. Louis, Mosby; 1990; 77-104.

Schüttler J, Stoeckel H, Schwilden H. Pharmacokinetic and pharmacodynamic modelling of propofol (Diprivan) in volunteers and surgical patients. *Postgraduate Medical Journal* 1985; **61**: Suppl 3; 53-54.

Schüttler J, Schwilden H, Stoeckel H. Pharmacokinetic-dynamic modeling of Diprivan. *Anesthesiology* 1986; **65**: A549.

Scott RPF, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. *Anaesthesia* 1988; **43**: 492-494.

Sereni F, Morselli P, Pardi G. Postnatal development of drug metabolism in human infants. In: Bossart H, Cruz JM, Huber A, eds. *Perinatal Medicine.* Bern, Huber Publishers; 1973; 63-77.

Shafer A, Doze VA, Shafer SL, White PF. Pharmacokinetics and pharmacodynamics of propofol infusions during general anaesthesia *Anesthesiology* 1988; **69**: 348-356.

Shafer SL, Siegel LC, Cooke JE, Scott JC. Testing computer-controlled infusion pumps by simulation. *Anesthesiology* 1988; **68**: 261-266.

Shafer SL. Recent developments in the pharmacokinetics and pharmacodynamics of intravenously administered anesthetic drugs. *Current Opinion in Anaesthesiology.* 1993; **6**: 625-630.

Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples) *Biometrika* 1965; **52**: 591-611.

Short SM, Aun CST. Haemodynamic effects of propofol in children. *Anaesthesia* 1991; 46: 783-785.

Short TG, Aun CST, Tan P, Wong J, Tam YH, Oh TE. A prospective evaluation of pharmacokinetic model controlled infusion of propofol in paediatric patients. *British Journal of Anaesthesia* 1994 : **72**: 302-306.

Shumaker RC. PKCALC: A BASIC interactive computer program for statistical and pharmacokinetic analysis of data. *Drug Metabolism Reviews* 1986; **17**: 331- 348

Simons PJ, Cockshott ID, Douglas EJ, Gordon EA, Hopkins K, Rowland M. Disposition in male volunteers of a subanaesthetic intravenous dose of an oil in water emulsion of ^{14}C- propofol. *Xenobiotica* 1988; 18: 429-440.

Skovsted P, Price ML, Price HL. The effects of short acting barbiturates on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. *Anesthesiology* 1970; 33: 10-18.

Skues MA, Prys-Roberts C. The pharmacology of propofol. *Journal of Clinical Anesthesia* 1989; **1**: (5) 387-400.

Slavik JR. Perioperative echocardiography *Anesthesiology Clinics of North America* 1988; **6**: No.4 : 769- 783.

Smith RM. Progress in paediatric anaesthesia in the United States. *Paediatric Anaesthesia* 1991; **1**: 65-73.

Snellen FT, Vanacker B, van Aken H. Propofol - nitrous oxide versus thiopental sodium - isoflurane - nitrous oxide for strabismus surgery in children. *Journal of Clinical Anesthesia* 1993; **5**: 37- 41.

Sonntag H, Hellberg K, Schenk HD, Donath U, Regensburger D, Kettler D, Duchanova H,Larsen R. Effects of thiopental (Trapanal) on coronary blood flow and myocardial metabolism in man. *Acta Anaesthesiologica Scandinavica* 1975; **19**: 69-78.

Sorbo S, Hudson RJ, Loomis JC. The Pharmacokinetics of thiopental in pediatric surgical patients. *Anesthesiology* 1984 ; **61** : 666 - 670

Stark RD, Binks SM, Dutka VN, O'Connor KM, Arnstein MJA, Glen JB. A review of the safety and tolerance of propofol ("Diprivan"). *Postgraduate Medical Journal* 1985; **61** (Suppl 3): 152-156.

Steegers PA, Foster PA. Propofol in total intravenous anaesthesia without nitrous oxide. *Anaesthesia* 1988; **43**: (Suppl): 94-97.

Steward DJ. A simplified scoring system for the postoperative recovery room. *Canadian Anaesthetists Society Journal* 1975; 22: No.1: 111-113.

Steward DJ. Daycare anaesthesia in paediatrics. In: *Proceedings of the First European Congress of Paediatric Anaesthesia*. 1986; Rotterdam.

Taylor MB, Grounds RM, Mulrooney PD, Morgan M. Ventilatory effects of propofol during induction of anaesthesia. Comparison with thiopentone. *Anaesthesia* 1986; **41**: 816-20.

Thomas JS, Boheimer NO. An isolated grand mal seizures 5 days after propofol anaesthesia. *Anaesthesia* 1991; **46**: 508.

Tibballs J, Osborne A, Hockmann M. A comparative study of cardiac output measurement by dye dilution and pulsed Doppler ultrasound. *Anaesthesia and Intensive Care* 1988a; **16**: 272-277.

Tibballs J, Malbezin S. Cardiovascular responses to induction of anaesthesia with thiopentone and suxamethonium in infants and children. *Anaesthesia and Intensive Care* 1988b; **16**: 278-284.

Trotter C, Serpell MG. Neurological sequelae in children after prolonged propofol infusion. *Anaesthesia* 1992, **47**: 340-342.

Turtle MJ, Cullen P, Prys-Roberts C, Coates D, Monk CR, Faroqui MH. Dose requirements of propofol by infusion during nitrous oxide anaesthesia in man II: patients premedicated with lorazepam. *British Journal of Anaesthesia* 1987, **59**: 283-287.

Valanne J, Korttila K. Comparison of methohexitone and propofol ("Diprivan") for induction of enflurane anaesthesia in outpatients. *Postgraduate Medical Journal* 1985; **61**: Suppl 3: 138-143.

Valtonen M, Iisalo E, Kanto J, Tikkanen J. Comparison between propofol and thiopentone for induction of anaesthesia in children. *Anaesthesia.* 1988; **43**: 696-699.

Valtonen M, Iisalo E, Kanto J, Rosenberg P. Propofol as an induction agent in children: pain on injection and pharmacokinetics. *Acta Anaesthesiologica Scandinavica* 1989a; **33** : 152 - 155

Valtonen M. Anaesthesia for computerised tomography of the brain in children: a comparison of propofol and thiopentone. *Acta Anaesthesiologica Scandinavica* 1989b; **33**: 170-173.

Vandermeersch E, Van Hemelrijck J, Byttebier G, Van Aken H. Pharmacokinetics of propofol during continuous infusion for pediatric anesthesia. *Acta Anaesthesiologica Belgica.* 1989; **40**: 161-165.

Vangerven M, Van Hemelrijck J, Wouters P, Vandermeersch E, Van Aken H. Light anaesthesia with propofol for paediatric MRI. *Anaesthesia* 1992; **47**: 706-707.

Veroli P, O'Kelly B, Bertrand F, Trouvin JH, Farinotti R, Ecoffey C. Extrahepatic metabolism of propofol in man during the anhepatic phase of orthotopic liver transplantation. *British Journal of Anaesthesia* 1992; **68**: 183-186.

Walmsley AJ, McLeod B, Ponte J. The new formulation of I.C.I. 35868 (propofol) as the main agent for minor surgical procedures. *European Journal of Anaesthesiology* 1986; **3**: 19-26.

Watcha MF, Simeon RM, White PF, Stevens JL. Effect of propofol on the incidence of postoperative vomiting after strabismus surgery in pediatric outpatients. *Anesthesiology* 1991; 75: 204-209.

Wear R, Robinson S, Gregory GA. The effect of halothane on the baroresponse of adult and baby rabbits. *Anesthesiology* 1982; 56: 188-191.

Weir PM, Munro HM, Reynolds PI, Lewis IH, Wilton NCT. Propofol infusion and the incidence of emesis in pediatric outpatient strabismus surgery. *Anesthesia and Analgesia* 1993; **76**: 760-764.

Westrin P, Jonmarker C, Werner O. Thiopental requirements for induction of anesthesia in neonates and in infants one to six months of age. *Anesthesiology* 1989; **71**: 344-346.

Westrin P. The induction dose of propofol in infants 1-6 months of age and in children 10-16 years of age. *Anesthesiology* 1991;**74**: 455-458.

White M, Kenny GNC. Intravenous propofol anaesthesia using a computerised infusion system. *Anaesthesia.* 1990; **45**: 204-209.

Widdowson EM. Changes in body proportions and composition during growth. In Davies JA, Dobbing J, eds. *Scientific Foundations of Paediatrics.* London, Heinmann Medical Books Ltd.; 1974; 153-163.

Wittenstein U, Lyle DJR. Fits after alfentanil and propofol. *Anaesthesia.* 1989; **44**: 532-533.

Wolf WJ, Neal MB, Peterson MD. The hemodynamic and cardiovascular effects of isoflurane and halothane anesthesia in children. *Anesthesiology* 1986; 64: 328-333.

Wood M. Plasma drug binding: Implications for anesthesiologists. *Anesthesia and Analgesia* 1986; **65**: 786-804.

Wood PR, Browne GPR, Pugh S. Propofol infusion for the treatment of status epilepticus. *Lancet* 1988; **1**: 480-481.

Yanny HF, Christmas D. Propofol infusions for status epilepticus. *Anaesthesia* 1988; **43**: 514.

SECTION VIII
APPENDICES

APPENDIX A

Acknowledgements

ACKNOWLEDGEMENTS

This thesis is, of course, my own work but I could not have completed it without help from many of my colleagues for which I am exceedingly grateful. However I should like to make particular mention of a few by name.

I wish to express my grateful thanks to Professor TE Oh for his stimulus and guidance during the research and writing of the thesis.

I owe much to Dr. TG Short who has been my major collaborator in the research projects, and who has taught me the essentials of computer-controlled infusion.

I am grateful to Dr. DHY Leung for his advice and assistance with the statistics.

I sincerely thank Miss Perpetua Tan for undertaking the propofol and protein-binding assay, and Dr. M Arumanayagam for the analysis of α_1 acid glycoprotein and albumin concentrations.

Mr YH Tam wrote the computer programs for the pharmacokinetic model infusion pump and performed the least squares regression on the data, and I am delighted to be able to thank him and also Dr. TA Lim for his assistance with the pharmacokinetic programs.

Dr. SM Short has collaborated in the dose response and dose effects studies on haemodynamics, and I am grateful for his forbearance during the data collection. I am also grateful to Dr. Rita YT Sung for her assistance with the Doppler echocardiographic measurements of cardiac parameters.

I also wish to thank Dr. K Chan for the developing and giving advice on the technique of propofol assay.

Mrs Yuen Man Rowbottom assisted with the assessment of psychomotor recovery and I applaud her patience and thank her for her help. I acknowledge gratefully the help of the nursing staff in the recovery ward for performing the recovery assessment.

The kind provision of propofol standards by Zeneca Pharmaceuticals is acknowledged and they also provided financial assistance towards the presentation of part of this work at the joint paediatric anaesthesia meeting in Basel organised by the Association of Paediatric Anaesthetists of Great Britain and Ireland (APA), L'Association des Anesthesistes-Reanimateurs Pediatriques d'Expression Francaise (ADARPEF), and Schweizerische Interessengruppe für Kinderanästhesie (SIK).

I acknowledge with thanks the funds provided by the University and Polytechnics Grants Committee to complete part of this research through the Research Committee of the Chinese University of Hong Kong.

Finally, but not the least, I thank the parents of the patients who allowed their children to take part in the study.

APPENDIX B

Calibration Data of Propofol

CALIBRATION DATA OF PROPOFOL

Chapter 2: Methods

Interassay variation of propofol (mean of 3 for each point)

Propofol conc ng.ml^{-1}	Peak height ratio Propofol / Internal standard (n= 3)							n	Mean	SD	CV %
	1	2	3	4	5	6	7				
50	0.110	0.110	0.110	0.120	0.100	0.100	0.112	7	0.109	0.007	6.43
100	0.230	0.210	0.210	0.200	0.230	0.210	0.211	7	0.215	0.011	5.25
250	0.410	0.440	0.460	0.510	0.530	0.540	0.518	7	0.487	0.050	10.27
500	0.950	0.970	0.950	0.940	0.990	1.010	1.069	7	0.983	0.045	4.62
1000	2.240	2.030	1.980	1.920	2.130	2.230	2.399	7	2.133	0.169	7.94
3000	6.240	5.850	6.700	5.930	6.030	5.820	6.444	7	6.145	0.331	5.39

Intra-assay variation (n=3)

Propofol conc ng.ml^{-1}	Peak height ratio Propofol /Internal standard			Mean	SD	CV %
	1	2	3			
50	0.104	0.127	0.121	0.120	0.010	9.96
100	0.199	0.209	0.207	0.210	0.010	2.64
250	0.473	0.515	0.529	0.510	0.030	5.77
500	0.936	0.968	0.929	0.940	0.020	2.19
1000	1.919	1.865	1.997	1.920	0.050	2.65
3000	5.931	6.031	5.817	5.930	0.110	1.81

APPENDIX C

Patient Data Tables

Patient Data Tables

Chapter 3: Induction dose requirement
Demographic and dose response data

Patient No	Age (yr)	Sex	B.wt (kg)	Dose group	Propofol dose (mg)	Surgery	Anxious	LER	AFM	Pain	Apnoea	Duration of apnoea (s)	Involuntary movements
299	0	M	9.3	1.2	11.2	Reimplantation of ureter	•	N	N	N	N	0	Y
239	1	M	12.2	1.2	15.0	Hypospadias repair	Y	N	N	N	N	0	N
284	1	M	10.7	1.2	13.0	Orchidopexy	Y	N	N	N	N	0	Y
248	1	M	9.0	1.2	11.0	Orchidopexy	Y	N	N	N	N	0	N
285	3	M	13.7	1.2	16.4	Herniotomy	N	N	N	N	N	0	Y
246	3	M	13.0	1.2	16.0	HLPPV	Y	N	N	Y	N	0	N
290	4	M	12.6	1.2	15.0	Orchidopexy	N	Y	Y	N	N	0	Y
228	4	F	13.5	1.2	16.2	Orthopaedic	Y	Y	Y	N	N	0	•
289	4	M	15.5	1.2	19.0	HLPPV	N	N	N	N	N	0	Y
295	4	M	16.0	1.2	19.2	Ex of thyroglossal cyst	Y	N	N	N	N	0	Y
288	4	M	17.8	1.2	21.5	Excision of naevus	N	N	N	N	N	0	Y
286	5	M	12.0	1.2	14.5	Herniotomy	N	N	N	N	N	0	Y
293	5	M	21.5	1.2	25.8	Orthopaedic	N	N	Y	N	Y	15	N
296	5	M	15.0	1.2	18.0	Orthopaedic	Y	N	N	N	N	0	Y
287	5	M	18.0	1.2	21.5	Circumcision	N	N	N	N	N	0	Y
244	6	F	14.2	1.2	17.0	Orthopaedic	N	Y	N	N	N	0	N
237	6	M	20.0	1.2	24.0	Testicular biopsy	•	N	N	N	N	0	•
235	6	M	22.0	1.2	24.6	Orthopaedic	Y	Y	N	N	N	0	•
247	6	M	18.7	1.2	22.4	Herniotomy	•	N	N	N	N	0	N
229	7	M	13.6	1.2	16.3	Orthopaedic	N	N	N	Y	N	0	•
297	8	M	31.0	1.2	37.0	Excision of lipoma	Y	Y	Y	N	N	0	Y
230	9	F	30.0	1.2	36.0	Orthopaedic	Y	N	N	N	N	0	Y
249	9	F	37.5	1.2	45.0	Orthopaedic	Y	Y	Y	N	N	0	Y
231	9	M	26.0	1.2	31.2	Orthopaedic	N	Y	N	Y	N	0	N
245	9	M	32.0	1.2	38.5	HLPPV	Y	N	N	N	N	0	N
298	9	F	22.5	1.2	27.0	Excision of ganglion	Y	Y	N	Y	N	0	Y
233	9	M	29.5	1.2	35.4	Dental extraction	Y	N	N	Y	N	0	•
292	10	M	31.8	1.2	38.2	Orthopaedic	N	N	Y	N	Y	22	Y
294	11	M	28.2	1.2	33.8	Orthopaedic	N	N	N	N	N	0	Y
300	12	M	36.9	1.2	44.3	Circumcision	N	N	N	N	N	0	Y
280	1	M	12.5	1.4	17.5	Closure of colostomy	Y	N	N	N	N	0	Y
281	1	M	7.8	1.4	10.9	Herniotomy	N	N	N	N	N	0	Y
291	1	F	11.0	1.4	15.4	Orthopaedic	Y	N	N	N	N	0	Y
251	2	M	13.0	1.4	18.2	HLPPV	N	N	N	N	N	0	Y
274	2	M	17.6	1.4	25.0	Testicular biopsy	Y	Y	N	N	N	0	Y
278	3	M	14.2	1.4	20.0	Herniotomy	•	Y	Y	Y	N	0	Y
275	3	M	16.5	1.4	23.0	Herniotomy	Y	N	N	N	N	0	Y
269	4	M	23.0	1.4	32.2	Herniotomy	N	N	N	N	N	0	Y
252	4	M	14.8	1.4	20.7	Circumcision	N	N	Y	N	N	0	Y
268	4	M	20.3	1.4	28.0	Herniotomy	Y	Y	N	Y	N	0	Y
270	4	F	15.4	1.4	21.6	Bil. herniotomy	N	N	N	N	N	0	Y
276	4	F	16.4	1.4	19.6	Herniotomy	N	Y	N	N	N	0	Y
266	4	M	15.0	1.4	21.0	HLPPV	N	N	Y	N	N	0	Y
273	5	F	14.8	1.4	20.7	Revision of scar	Y	N	N	N	N	0	Y
253	5	M	15.7	1.4	22.0	Herniotomy	N	Y	N	Y	N	0	Y
254	5	M	17.6	1.4	24.6	Herniotomy & circumcision	N	N	N	N	N	0	Y
271	6	M	19.0	1.4	26.6	Herniotomy	N	N	N	N	N	0	Y
277	6	M	15.8	1.4	22.0	Herniotomy	N	N	N	Y	N	0	Y
282	7	M	29.6	1.4	39.4	Hypospadias repair	N	N	Y	N	Y	23	Y
261	7	M	23.7	1.4	32.5	Herniotomy & circumcision	N	N	N	N	N	0	N
283	7	F	20.6	1.4	28.8	Excision of lesion	N	N	N	N	N	0	Y
257	7	M	21.2	1.4	29.7	Herniotomy	N	Y	Y	N	Y	35	N
255	7	M	26.3	1.4	36.8	Herniotomy	N	N	N	N	N	0	Y
260	8	M	24.0	1.4	34.0	Herniotomy	•	Y	Y	N	N	0	Y
259	8	M	27.0	1.4	38.0	Herniotomy	N	N	N	N	N	0	Y
279	8	F	26.0	1.4	36.5	Orthopaedic	•	Y	Y	N	N	0	Y
264	9	M	26.0	1.4	36.4	Orthopaedic	N	N	N	N	N	0	N
272	11	M	26.6	1.4	37.0	Herniotomy	N	Y	Y	N	N	0	Y
258	11	M	46.0	1.4	65.0	Excision of scalp lesion	Y	N	N	N	N	0	Y
191	1	M	6.5	1.6	10.4	Pyeloplasty	Y	N	N	N	N	0	N
126	1	M	9.9	1.6	16.0	Herniotomy	Y	N	N	N	N	0	N
243	1	M	9.9	1.6	15.8	Closure of colostomy	Y	N	N	N	N	0	Y
222	1	M	9.2	1.6	14.7	Rectal biopsy	Y	N	N	N	N	0	Y
216	1	F	9.8	1.6	15.7	Orthopaedic	N	N	N	Y	N	0	Y
143	1	M	10.5	1.6	16.8	Herniotomy	N	N	N	N	N	0	Y
82	1	M	9.4	1.6	16.0	Orchidopexy	Y	N	N	•	N	0	Y
69	2	M	15.6	1.6	25.0	Excision of cyst	Y	N	N	•	Y	12	Y
195	2	F	10.0	1.6	16.0	Orthopaedic	Y	Y	Y	Y	Y	14	N

Chapter 3: Induction dose requirement
Demographic and dose response data (continued)

Patient No	Age (yr)	Sex	B.wt (kg)	Dose group	Propofol dose (mg)	Surgery	Anxious	LER	AFM	Pain	Apnoea	Duration of apnoea (s)	Involuntary movements
115	2	M	11.6	1.6	19.0	Circumcision	N	N	N	N	N	0	Y
79	3	F	16.1	1.6	26.0	Herniotomy	N	Y	Y	•	Y	20	N
232	3	F	10.0	1.6	16.0	Excision of lymph node	N	N	N	N	N	0	Y
242	3	M	15.4	1.6	24.6	Hypospadias repair	N	N	N	N	N	0	Y
178	3	M	21.5	1.6	35.0	Orthopaedic	Y	Y	N	N	N	0	N
43	3	M	13.8	1.6	22.0	Herniotomy	N	Y	N	N	Y	10	N
240	4	M	17.4	1.6	27.8	Circumcision	N	N	N	N	N	0	Y
189	4	M	13.2	1.6	21.1	Herniotomy	N	Y	N	N	N	0	Y
19	4	F	14.6	1.6	24.0	Reimplantation of ureters	N	N	Y	Y	Y	24	Y
265	5	M	15.1	1.6	24.2	Excision of cyst	N	N	N	N	N	0	Y
105	5	M	21.0	1.6	33.5	Herniotomy	N	Y	Y	N	Y	20	Y
114	5	M	17.4	1.6	27.8	Ex preauricular sinus	Y	N	N	Y	N	0	N
108	5	M	17.7	1.6	28.0	Herniotomy	Y	Y	Y	N	N	0	N
234	5	M	19.0	1.6	30.4	Herniotomy	N	N	N	Y	N	0	Y
267	5	F	19.0	1.6	30.4	Bil. herniotomy	N	N	Y	Y	N	0	Y
10	5	M	24.0	1.6	38.5	Circumcision	N	N	N	•	N	0	Y
85	6	M	18.7	1.6	30.0	HLPPV	N	N	N	N	N	0	Y
224	6	M	21.1	1.6	34.0	Orthopaedic	Y	Y	Y	N	N	0	Y
46	6	M	20.6	1.6	32.9	Orthopaedic	N	Y	Y	Y	N	0	Y
215	7	M	20.4	1.6	32.6	Testicular biopsy	N	N	Y	Y	Y	25	N
138	7	M	25.3	1.6	40.5	Circumcision	N	Y	Y	N	Y	20	N
49	7	M	18.7	1.6	30.0	Herniotomy	N	Y	Y	N	Y	18	Y
131	8	M	24.6	1.6	40.0	Excision of cyst	N	Y	N	N	N	0	N
256	8	M	22.9	1.6	26.6	Herniotomy	N	N	N	N	N	0	Y
159	8	M	30.0	1.6	48.0	HLPPV	N	Y	Y	N	N	0	Y
172	9	M	37.6	1.6	60.0	Herniotomy	N	Y	N	N	N	0	Y
241	9	M	25.0	1.6	40.0	Ex of prolapsed anus	N	N	N	N	N	0	Y
120	9	F	28.0	1.6	45.0	Herniotomy	Y	Y	Y	N	N	0	N
4	9	M	27.0	1.6	43.0	Orthopaedic	•	Y	N	N	Y	5	Y
95	9	M	30.0	1.6	48.0	Herniotomy	N	Y	Y	N	Y	12	Y
17	10	M	53.7	1.6	85.0	Orthopaedic	Y	Y	Y	N	Y	20	Y
185	10	M	28.0	1.6	45.0	Exploration of toe	N	Y	Y	N	N	0	N
42	10	M	32.4	1.6	51.8	Circumcision	N	Y	Y	N	Y	39	Y
29	10	M	28.9	1.6	46.2	Excision of wart	N	N	Y	Y	N	0	Y
148	11	M	27.5	1.6	44.0	OGD	N	N	N	N	N	0	Y
199	12	M	43.0	1.6	68.0	Circumcision	Y	Y	Y	N	N	0	N
144	1	M	10.2	1.8	18.3	Orthopaedic	Y	N	Y	N	N	0	N
23	1	M	10.2	1.8	18.4	Orchidopexy	N	Y	N	N	N	0	Y
170	1	M	10.2	1.8	18.4	Herniotomy	Y	Y	Y	N	N	0	Y
223	1	F	9.4	1.8	16.9	Cleft palate repair	Y	N	N	N	N	0	Y
18	1	M	12.0	1.8	22.0	Orchidopexy	Y	Y	N	Y	N	0	N
52	1	M	11.0	1.8	20.0	Herniotomy	Y	Y	Y	•	N	0	N
109	2	M	10.5	1.8	18.9	Removal of ear wax	Y	N	N	N	N	0	N
31	2	M	9.7	1.8	17.5	Orchidopexy	N	N	N	Y	N	0	Y
81	2	M	10.6	1.8	19.1	Drainage of abscess	N	Y	Y	Y	Y	17	Y
110	3	M	13.2	1.8	24.0	Excision of auricle	N	N	N	N	N	0	N
176	3	M	16.5	1.8	29.8	Herniotomy	N	Y	Y	Y	N	0	N
194	3	M	16.0	1.8	28.8	Herniotomy	N	Y	Y	N	N	0	Y
11	4	M	16.7	1.8	30.0	Circumcision	N	Y	Y	N	N	0	N
45	4	M	14.5	1.8	26.0	Herniotomy	N	N	Y	N	Y	18	Y
173	4	M	16.0	1.8	28.8	HLPPV	N	Y	Y	N	Y	19	Y
206	4	M	17.2	1.8	31.0	HLPPV	Y	Y	Y	N	Y	60	Y
101	4	M	15.8	1.8	28.0	Circumcision	Y	N	N	N	Y	•	Y
100	5	M	15.0	1.8	27.0	Herniotomy	N	Y	Y	Y	N	0	Y
211	6	M	14.8	1.8	26.7	Circumcision	N	Y	Y	N	Y	18	Y
89	6	M	18.5	1.8	34.0	Orthopaedic	N	N	Y	N	N	0	Y
88	6	M	23.1	1.8	42.0	Orthopaedic	N	N	Y	N	N	0	N
139	6	M	20.0	1.8	36.0	Herniotomy	N	Y	Y	N	Y	32	Y
53	7	F	24.4	1.8	44.0	Sigmoidoscopy	N	Y	Y	•	Y	23	Y
166	7	M	20.0	1.8	36.0	Orthopaedic	N	Y	Y	N	N	0	N
1	8	M	22.4	1.8	40.0	Circumcision	N	N	N	N	N	0	Y
40	8	M	24.0	1.8	43.2	Orthopaedic	N	Y	Y	Y	Y	20	Y
180	9	F	25.4	1.8	46.0	Excision of skin lump	Y	Y	Y	Y	N	0	N
134	9	M	39.5	1.8	71.1	Orchidopexy	N	N	N	N	N	0	Y
50	9	M	27.0	1.8	49.0	Circumcision	N	Y	Y	•	Y	11	N
132	10	M	25.8	1.8	46.4	Herniotomy	N	Y	Y	N	Y	16	N
151	10	M	37.0	1.8	66.6	Orthopaedic	Y	Y	Y	N	N	0	N
15	11	M	31.5	1.8	57.6	Ligation of varicocoele	•	Y	Y	N	Y	27	Y

Chapter 3: Induction dose requirement
Demographic and dose response data (continued)

Patient No	Age (yr)	Sex	B.wt (kg)	Dose group	Propofol dose (mg)	Surgery	Anxious	LER	AFM	Pain	Apnoea	Duration of apnoea (s)	Involuntary movements
93	11	M	33.5	1.8	60.0	Circumcision	N	Y	Y	N	Y	28	Y
41	11	M	37.1	1.8	66.7	Herniotomy	Y	Y	Y	•	N	0	Y
171	11	M	41.0	1.8	74.0	Urethral dilatation	N	N	Y	N	Y	48	N
212	1	M	10.5	2.0	21.0	Orchidopexy	Y	N	Y	N	N	0	Y
83	1	M	10.4	2.0	20.0	Hypospadias repair	Y	Y	Y	N	Y	•	N
141	1	M	13.4	2.0	26.8	Excision of cyst	Y	Y	N	Y	N	0	Y
227	1	M	8.6	2.0	17.2	Herniotomy	Y	Y	Y	N	N	0	N
226	1	M	10.0	2.0	20.0	Herniotomy	N	Y	Y	N	N	0	N
68	1	M	11.0	2.0	22.0	Herniotomy	N	N	N	N	N	0	Y
197	1	F	8.0	2.0	16.0	Herniotomy	Y	Y	Y	N	Y	60	N
160	1	M	11.0	2.0	22.0	Herniotomy	Y	Y	Y	•	N	0	N
74	2	M	11.8	2.0	23.6	Orchidopexy	Y	Y	Y	N	Y	30	N
75	2	F	9.7	2.0	19.4	Epigastric hernia repair	N	Y	Y	N	N	0	Y
238	2	M	12.4	2.0	25.0	Herniotomy	Y	Y	Y	N	N	0	N
201	2	M	13.5	2.0	27.0	Herniotomy	Y	Y	Y	N	N	0	N
208	2	M	13.6	2.0	27.2	Herniotomy	N	Y	Y	N	N	0	N
236	2	M	11.7	2.0	24.0	Herniotomy	Y	Y	Y	N	Y	35	•
209	3	M	16.0	2.0	32.0	HLPPV	N	Y	Y	N	N	0	Y
63	3	M	13.7	2.0	27.5	Circumcision	N	Y	Y	•	N	0	Y
99	3	M	19.0	2.0	38.0	Herniotomy	N	Y	Y	N	Y	21	N
97	4	M	15.0	2.0	30.0	Circumcision	N	Y	Y	N	Y	14	Y
70	4	M	18.0	2.0	36.0	Circumcision	N	Y	Y	Y	Y	25	Y
62	4	M	14.7	2.0	29.5	Circumcision	Y	Y	Y	N	Y	•	Y
55	4	F	17.0	2.0	34.0	Repair of vaginal fistula	N	Y	Y	N	N	0	Y
177	4	M	14.0	2.0	28.0	Excision of penile fistula	N	Y	Y	N	N	0	N
165	5	M	17.0	2.0	34.0	Circumcision	N	Y	Y	Y	Y	30	Y
103	5	M	19.0	2.0	38.0	Herniotomy	N	Y	Y	N	Y	35	Y
262	5	M	21.0	2.0	42.0	Herniotomy	Y	Y	Y	Y	N	0	Y
250	5	M	21.0	2.0	43.0	Orthopaedic	Y	N	N	Y	Y	120	Y
263	5	M	18.0	2.0	36.0	Circumcision	N	Y	Y	Y	N	0	N
116	6	F	19.0	2.0	38.0	Excision of cyst	N	Y	Y	N	Y	18	Y
94	6	M	16.5	2.0	33.0	Circumcision	N	Y	Y	Y	Y	28	Y
181	6	F	16.6	2.0	33.0	Herniotomy	N	Y	Y	N	Y	35	N
33	6	M	20.7	2.0	41.4	HLPPV	N	Y	Y	Y	Y	24	N
92	6	M	18.5	2.0	37.0	Hypospadias repair	N	Y	Y	Y	N	0	Y
135	7	F	18.0	2.0	36.0	Excision of cyst	N	Y	Y	N	Y	10	N
183	7	M	21.4	2.0	42.8	Circumcision	N	Y	Y	N	Y	30	Y
111	7	M	24.4	2.0	49.0	Herniotomy	Y	Y	Y	N	N	0	N
87	8	F	27.7	2.0	55.0	Orthopaedic	Y	Y	Y	N	Y	•	N
13	8	M	23.6	2.0	57.0	Circumcision	N	Y	Y	Y	Y	17	N
3	8	M	26.2	2.0	52.0	Orthopaedic	N	N	Y	N	N	0	Y
113	10	M	42.0	2.0	84.0	Excision of mole	N	Y	Y	N	N	0	N
107	10	M	26.3	2.0	52.6	Circumcision	N	Y	Y	N	Y	44	N
30	10	M	30.9	2.0	62.0	Turbinectomy	N	Y	Y	•	Y	22	Y
133	10	M	29.0	2.0	58.0	Ex of preauricular sinus	N	Y	Y	Y	Y	38	N
129	10	F	33.5	2.0	67.0	Ex of duplex kidney	N	Y	Y	N	Y	17	N
20	11	F	37.0	2.0	74.0	Excision of cyst	N	Y	Y	Y	Y	24	Y
84	11	F	26.2	2.0	52.0	Orthopaedic	N	Y	Y	N	Y	10	Y
225	1	F	10.0	2.2	22.0	Herniotomy	•	Y	N	N	N	0	N
118	1	M	10.7	2.2	23.5	Excision of lipoma	Y	Y	N	Y	N	0	N
128	1	M	11.0	2.2	24.0	Orchidopexy	Y	Y	Y	Y	Y	22	Y
119	1	F	8.8	2.2	20.0	Herniotomy	Y	Y	Y	Y	Y	23	Y
202	1	M	10.0	2.2	22.0	Orthopaedic	Y	Y	Y	N	N	0	N
221	1	M	8.9	2.2	19.5	Orchidopexy	Y	Y	Y	N	N	0	N
27	1	M	10.4	2.2	22.9	HLPPV	Y	Y	Y	N	N	0	N
67	2	F	13.7	2.2	30.0	Herniotomy	Y	N	N	Y	N	0	Y
28	2	F	10.9	2.2	24.0	Herniotomy	Y	Y	Y	N	Y	22	Y
157	2	M	16.6	2.2	33.0	Herniotomy	Y	Y	Y	N	Y	14	Y
7	2	M	11.1	2.2	24.4	Hypospadias repair	N	Y	Y	N	Y	19	N
58	2	M	13.8	2.2	30.0	Herniotomy	N	Y	Y	•	Y	21	N
184	3	M	14.2	2.2	31.0	Circumcision	Y	Y	Y	N	Y	15	N
198	3	F	15.0	2.2	33.0	Herniotomy	Y	Y	N	N	N	0	Y
164	3	M	13.4	2.2	29.5	Correction of deformed ear	N	Y	Y	Y	N	0	N
65	4	M	17.0	2.2	37.4	HLPPV	N	Y	Y	N	Y	21	N
188	4	M	16.9	2.2	37.2	Circumcision	N	Y	Y	Y	N	0	N
56	4	M	13.0	2.2	29.0	Circumcision	N	Y	N	N	Y	17	Y
179	4	M	15.4	2.2	34.0	Circumcision	Y	Y	Y	N	N	0	N
90	5	F	19.0	2.2	42.0	Herniotomy	N	N	Y	N	Y	17	Y

Chapter 3: Induction dose requirement
Demographic and dose response data (continued)

Patient No	Age (yr)	Sex	B.wt (kg)	Dose group	Propofol dose (mg)	Surgery	Anxious	LER	AFM	Pain	Apnoea	Duration of apnoea (s)	Involuntary movements
155	5	M	16.8	2.2	37.0	Circumcision	N	Y	N	N	N	0	Y
187	6	M	22.7	2.2	49.9	Herniotomy	Y	Y	Y	N	N	0	N
123	7	M	20.6	2.2	45.0	Herniotomy	•	Y	Y	N	N	0	N
91	7	M	21.2	2.2	47.0	HLPPV	N	Y	Y	N	Y	15	N
190	7	M	26.3	2.2	57.9	Herniotomy	N	Y	Y	Y	N	0	Y
130	7	F	20.5	2.2	45.0	Herniotomy	N	Y	Y	N	Y	12	Y
5	7	M	20.0	2.2	44.0	Herniotomy	N	Y	Y	N	Y	14	Y
37	8	M	30.0	2.2	66.0	Orthopaedic	N	Y	Y	Y	Y	10	N
47	8	M	29.0	2.2	64.0	Orthopaedic	N	•	•	•	•	0	N
32	8	M	34.0	2.2	74.8	Herniotomy	Y	Y	Y	Y	N	0	Y
14	8	M	46.0	2.2	101.2	Circumcision	N	Y	Y	N	N	0	Y
175	9	F	24.0	2.2	53.0	Herniotomy	N	Y	Y	N	N	0	N
2	9	M	24.4	2.2	54.0	Penile chordae	N	Y	Y	N	N	0	Y
66	10	M	22.0	2.2	48.0	Herniotomy	N	Y	Y	Y	Y	12	N
39	10	F	22.4	2.2	49.3	Orthopaedic	Y	Y	Y	N	N	0	N
149	11	M	44.3	2.2	97.5	Herniotomy	N	Y	N	N	N	0	Y
140	11	M	23.5	2.2	52.0	Circumcision	N	N	Y	Y	Y	92	Y
218	11	M	38.5	2.2	84.7	Circumcision	N	Y	Y	N	N	0	Y
161	0	M	7.8	2.4	18.7	HLPPV	Y	N	N	•	N	0	N
35	1	M	11.9	2.4	28.6	Herniotomy	Y	Y	Y	N	N	0	Y
168	1	M	9.0	2.4	21.6	Orthopaedic	Y	Y	Y	N	Y	•	N
104	1	M	9.2	2.4	22.0	Orchidopexy	Y	Y	Y	N	N	0	N
127	1	M	9.8	2.4	23.5	Excision of auricle	Y	Y	Y	N	Y	20	Y
150	1	F	8.1	2.4	19.5	Anoplasty	Y	Y	Y	Y	Y	17	N
142	1	M	13.3	2.4	32.0	Division of tongue tie	Y	Y	Y	N	N	0	N
167	2	F	11.5	2.4	27.6	Anoplasty	N	Y	Y	N	Y	30	Y
77	2	M	12.6	2.4	30.0	Herniotomy	N	Y	Y	N	Y	30	Y
156	2	M	12.5	2.4	30.0	Ex of preauricular sinus	Y	Y	Y	N	Y	14	Y
152	2	F	13.9	2.4	33.3	Removal of foreign body	Y	Y	Y	Y	Y	50	N
73	2	M	12.5	2.4	30.0	Herniotomy	Y	Y	Y	N	N	0	N
54	2	M	12.2	2.4	26.0	Orchidopexy	Y	Y	Y	N	N	0	Y
76	2	M	14.4	2.4	34.5	Orchidopexy	N	Y	Y	Y	N	0	Y
153	3	M	15.3	2.4	37.0	Herniotomy	Y	Y	Y	Y	Y	100	N
9	3	M	15.8	2.4	38.0	Ex preauricular sinus	N	Y	N	N	N	0	Y
158	3	M	19.4	2.4	46.5	Herniotomy	Y	Y	Y	N	Y	135	N
174	4	M	16.0	2.4	38.4	Circumcision	N	Y	Y	N	N	0	Y
163	4	F	17.2	2.4	41.0	Excision of mole	N	Y	Y	N	Y	12	N
71	5	F	15.5	2.4	36.0	Excision of haemangioma	N	Y	Y	N	Y	24	N
51	5	M	21.0	2.4	50.0	Circumcision	N	Y	Y	Y	Y	18	Y
6	5	M	18.0	2.4	43.0	Herniotomy	N	Y	N	N	Y	•	Y
112	5	F	21.4	2.4	50.0	Ex epidermoid cyst	N	Y	Y	N	Y	11	N
61	5	M	17.5	2.4	42.0	Herniotomy	N	Y	Y	N	N	0	Y
86	6	F	18.9	2.4	45.0	Herniotomy	Y	Y	Y	N	Y	33	N
72	6	F	19.5	2.4	46.0	Herniotomy	Y	Y	Y	N	Y	53	Y
192	6	M	18.7	2.4	45.0	Circumcision	Y	Y	Y	Y	N	0	Y
196	6	F	18.8	2.4	45.0	Cystoscopy	N	Y	Y	Y	N	0	Y
200	7	M	20.5	2.4	50.0	Excision of cyst	N	Y	Y	N	Y	35	N
122	7	M	20.0	2.4	48.0	Herniotomy	•	Y	Y	Y	N	0	N
59	7	M	19.6	2.4	48.0	Herniotomy	•	Y	Y	Y	N	0	Y
146	8	M	24.0	2.4	58.6	Herniotomy	N	Y	N	N	N	0	Y
124	8	F	26.9	2.4	65.0	Excision of cyst	N	Y	Y	N	Y	17	Y
186	8	F	29.0	2.4	69.6	Excision of lipoma	N	Y	Y	N	N	0	N
22	9	M	23.8	2.4	57.0	Hypospadias repair	N	Y	Y	N	Y	43	N
21	9	M	27.0	2.4	65.0	Hypospadias repair	N	Y	Y	Y	Y	18	Y
154	9	F	20.0	2.4	48.0	Herniotomy	N	Y	Y	N	N	0	Y
12	9	M	32.7	2.4	78.5	HLPPV	Y	Y	Y	Y	N	0	Y
182	10	M	49.6	2.4	119.0	Circumcision	•	Y	Y	N	Y	70	Y
25	10	M	26.0	2.4	62.4	Orthopaedic	N	Y	Y	N	Y	10	N
98	11	M	28.4	2.4	68.0	Circumcision	N	Y	Y	N	Y	15	Y
136	12	F	24.4	2.4	58.0	Herniotomy	N	Y	Y	N	N	0	Y
125	1	M	10.4	2.6	27.0	Orchidopexy	N	Y	Y	N	N	0	N
36	1	F	9.0	2.6	23.4	Orthopaedic	Y	Y	Y	N	Y	10	N
169	1	M	9.9	2.6	26.0	Pull through	Y	Y	Y	N	N	0	N
203	1	M	9.4	2.6	24.4	Orchidopexy	Y	Y	Y	N	N	0	Y
121	1	F	9.7	2.6	25.3	Excision of cyst	N	Y	Y	N	N	0	N
64	1	M	11.6	2.6	30.5	Division of tongue tie	Y	Y	Y	N	Y	64	Y
210	2	M	10.3	2.6	26.7	Hypospadias repair	Y	Y	Y	N	N	0	Y
207	2	M	16.8	2.6	43.7	Herniotomy	Y	Y	Y	N	Y	12	N

Chapter 3: Induction dose requirement
Demographic and dose response data (continued)

Patient No	Age (yr)	Sex	B.wt (kg)	Dose group	Propofol dose (mg)	Surgery	Anxious	LER	AFM	Pain	Apnoea	Duration of apnoea (s)	Involuntary movements
48	2	M	14.7	2.6	38.2	Orchidopexy	N	Y	Y	N	N	0	Y
34	2	M	14.8	2.6	38.5	Herniotomy	Y	Y	Y	N	Y	12	N
26	3	M	13.3	2.6	34.6	Orthopaedic	N	Y	N	•	Y	15	Y
44	3	M	17.4	2.6	45.0	Circumcision	Y	Y	Y	N	N	0	N
193	4	M	19.6	2.6	51.0	Herniotomy	N	Y	Y	N	Y	26	Y
162	4	F	19.2	2.6	50.0	Excision of mole	N	Y	Y	Y	N	0	Y
102	4	M	19.8	2.6	52.0	HLPPV	N	Y	Y	N	Y	40	N
214	4	F	18.0	2.6	46.8	Excision of sinus	N	Y	Y	N	Y	25	Y
60	4	M	14.6	2.6	38.0	Herniotomy	Y	Y	Y	•	N	0	Y
80	4	F	16.0	2.6	42.0	Herniotomy	N	Y	Y	N	Y	16	N
8	5	M	16.4	2.6	40.0	Excision of cyst	Y	Y	Y	N	N	0	Y
57	6	M	23.4	2.6	61.0	Herniotomy	•	Y	Y	N	Y	25	Y
220	6	M	23.0	2.6	60.0	Circumcision	N	Y	Y	N	N	0	Y
24	6	M	34.0	2.6	88.4	Orthopaedic	N	Y	Y	Y	N	0	Y
137	6	F	22.4	2.6	58.0	Herniotomy	Y	Y	Y	N	N	0	N
145	7	M	21.8	2.6	57.0	Herniotomy	N	Y	Y	N	Y	35	N
205	7	F	26.2	2.6	68.1	Excision of cyst	N	Y	Y	N	Y	22	N
117	8	M	29.0	2.6	75.0	Circumcision	N	Y	Y	Y	Y	41	N
78	8	M	23.4	2.6	60.8	Excision of papilloma	N	Y	Y	N	Y	10	N
147	8	M	35.0	2.6	91.0	Herniotomy	N	Y	Y	N	N	0	N
213	8	M	20.0	2.6	52.0	Orchidopexy	N	Y	Y	N	N	0	N
106	9	M	26.2	2.6	68.0	Circumcision	N	Y	Y	N	Y	40	N
38	9	M	22.0	2.6	57.4	Orthopaedic	N	Y	Y	•	Y	22	Y
219	10	F	33.0	2.6	85.8	Excision of colonic polyp	N	Y	Y	Y	N	0	N
96	10	M	30.5	2.6	80.0	Circumcision	N	Y	Y	N	Y	28	Y
204	11	M	34.1	2.6	88.7	Circumcision	N	Y	Y	N	Y	27	N
16	11	M	31.3	2.6	81.4	Circumcision	N	Y	Y	N	Y	25	N
217	12	F	41.0	2.6	106.6	Excision of colonic polyp	N	Y	Y	N	N	0	N

CHAPTER 4 : Influence of propofol dose on haemodynamic changes
Systolic, mean and diastolic arterial pressure data

Patients No	age (yr)	B wt (kg)	Dose group	Propofol dose (mg)	Mean arterial pressure (mmHg) Minutes after induction						Systolic arterial pressure (mmHg) Minutes after induction						Diastolic arterial pressure (mmHg) Minutes after induction						Pulse rate (bpm) Minutes after induction					
					0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
105	5	21.0	1.6	33.6	84	66	62	53	51	52	115	107	97	91	85	84	69	43	47	38	39	37	90	105	90	83	79	79
95	9	30.0	1.6	48.0	80	78	73	64	62	61	117	107	95	94	92	90	73	63	50	48	48	45	75	86	82	75	71	68
85	6	18.7	1.6	29.9	65	80	67	52	57	57	127	127	96	97	93	93	53	58	50	39	41	41	98	108	78	71	72	69
108	5	17.7	1.6	28.3	105	82	66	64	56	58	123	122	97	92	90	86	85	73	51	48	45	47	87	102	86	80	77	77
120	9	28.0	1.6	44.8	95	74	65	72	61	57	115	106	95	100	90	90	81	59	51	57	47	46	104	102	90	89	78	78
115	2	11.6	1.6	18.6	85	105	72	66	67	70	110	131	95	93	94	93	67	85	61	52	51	54	133	146	119	111	105	102
114	5	17.4	1.6	27.8	101	71	65	62	61	65	116	99	94	87	82	86	82	59	54	46	50	55	120	104	93	81	87	85
46	6	20.6	1.6	33.0	65	55	62	58	52	52	95	91	88	87	80	80	49	44	47	43	38	39	59	63	88	64	58	57
43	3	13.8	1.6	22.1	77	70	57	57	52	52	108	104	85	82	79	78	57	60	46	44	41	38	92	104	79	77	78	75
42	10	32.4	1.6	51.8	85	66	74	80	70	72	121	97	107	114	105	105	66	51	56	59	53	53	68	92	87	101	69	68
49	7	18.7	1.6	29.9	97	73	73	62	58	57	126	107	99	95	92	93	79	58	56	45	45	40	101	93	96	72	78	71
82	1	9.4	1.6	15.0	71	62	58	74	53	56	100	95	79	80	78	77	54	46	43	55	38	40	178	111	110	104	113	111
79	3	16.1	1.6	25.8	81	58	57	52	49	48	110	103	92	80	83	81	58	42	42	38	36	36	120	117	97	94	84	85
69	2	15.6	1.6	25.0	131	83	75	65	58	62	138	106	103	99	91	88	106	65	58	51	45	46	174	136	127	113	110	101
126	1	9.9	1.6	15.8	80	62	57	58	61	56	109	94	78	71	81	80	74	50	48	46	47	42	170	101	108	113	111	117
191	1	6.5	1.6	10.4	114	71	72	63	45	68	145	93	102	91	49	79	98	58	53	47	40	63	174	120	119	115	115	113
189	4	13.2	1.6	21.1	72	54	85	60	51	51	91	84	94	86	75	70	52	48	71	46	38	42	68	88	127	92	75	71
185	10	28.0	1.6	44.8	85	77	70	61	61	63	114	112	103	95	94	96	60	55	50	45	43	46	84	97	78	74	77	71
195	2	10.0	1.6	16.0	118	70	61	53	55	60	137	91	87	78	80	75	103	53	49	41	41	44	166	83	111	105	102	104
216	1	9.8	1.6	15.7	75	64	61	60	56	61	105	82	90	83	80	80	59	47	44	43	40	43	144	127	127	120	122	115
215	7	20.4	1.6	32.6	88	73	68	64	61	63	112	101	96	90	87	87	75	60	56	53	52	50	92	91	101	92	93	93
199	12	43.0	1.6	68.8	72	74	65	60	61	65	105	102	95	90	91	88	52	60	52	47	46	49	104	87	78	72	75	72
143	0	10.5	1.6	16.8	72	66	65	70	64	70	97	86	90	96	90	95	54	53	48	50	47	53	125	111	122	125	125	127
138	7	25.3	1.6	40.5	97	76	63	57	66	60	126	109	100	95	91	83	80	57	48	45	49	46	108	122	92	81	81	78
131	8	24.6	1.6	39.4	71	71	58	58	64	67	112	92	93	90	88	96	49	49	42	40	46	46	110	97	78	76	72	78
148	11	27.5	1.6	44.0	81	80	61	58	55	55	109	104	100	94	91	90	70	61	43	45	41	40	94	81	65	61	60	62
178	3	21.5	1.6	34.4	82	72	62	61	60	57	113	96	93	88	76	82	66	62	53	51	52	50	111	104	97	97	98	98
172	9	37.6	1.6	60.2	82	71	67	63	67	66	113	100	101	100	90	93	67	60	54	51	51	49	86	107	104	86	84	82
159	8	30.0	1.6	48.0	84	80	77	75	67	66	114	113	105	104	96	95	55	58	62	53	48	47	76	79	96	96	72	74
4	9	27.0	1.6	43.2	87	68	86	75	72	75	122	105	120	106	105	99	73	53	70	56	55	53	101	102	115	85	81	81
19	4	14.6	1.6	23.4	95	76	75	63	52	57	122	117	102	88	82	82	79	101	57	49	43	43	113	59	91	82	73	70
29	10	28.5	1.6	45.6	73	75	74	64	71	68	105	98	98	93	98	98	55	58	56	48	54	52	54	89	64	55	64	64
10	5	24.0	1.6	38.4	76	62	57	62	57	54	109	96	105	102	98	91	55	48	47	43	43	37	110	93	88	81	92	83
17	10	53.7	1.6	85.9	89	82	82	89	82	76	127	112	112	111	112	112	70	62	54	63	62	60	80	97	98	92	88	76
176	3	16.5	1.8	29.7	96	80	66	60	53	54	122	123	79	86	83	83	81	65	57	40	40	41	100	107	82	79	70	66
173	4	16.0	1.8	28.8	75	57	64	57	57	54	106	71	87	87	83	83	56	52	47	43	44	41	84	105	91	92	80	79
89	6	18.5	1.8	33.3	77	66	67	63	67	62	108	96	97	93	97	91	58	43	44	48	48	46	105	119	111	107	96	97
88	6	23.1	1.8	41.6	79	59	61	53	56	52	111	98	92	90	86	89	52	47	49	42	37	37	108	107	93	79	75	78
180	9	25.4	1.8	45.7	94	77	77	71	71	70	142	106	109	102	100	100	77	53	53	50	52	51	147	120	108	101	98	94
170	1	10.2	1.8	18.4	117	88	65	65	61	60	129	116	73	92	87	91	87	68	57	52	47	46	187	166	129	131	127	117
171	11	41.0	1.8	73.8	86	64	68	66	62	64	106	90	92	87	98	93	67	48	53	49	46	46	120	125	111	110	105	104
166	7	20.0	1.8	36.0	66	61	56	53	53	52	101	98	99	98	94	91	51	49	40	38	38	39	101	96	91	87	84	86
23	1	10.2	1.8	18.4	66	53	54	49	50	50	93	77	90	75	73	77	50	43	42	37	36	36	133	141	129	115	113	117
81	2	10.6	1.8	19.1	91	77	57	51	51	55	127	115	88	80	79	77	75	56	48	42	43	45	97	86	93	86	87	85

CHAPTER 4 : Influence of propofol dose on haemodynamic changes
Systolic, mean and diastolic arterial pressure data (continued)

Patients	age	B wt	Dose	Propofol	Mean arterial pressure (mmHg)						Systolic arterial pressure (mmHg)						Diastolic arterial pressure (mmHg)						Pulse rate (bpm)					
No			group	dose	Minutes after induction						Minutes after induction						Minutes after induction						Minutes after induction					
	(yr)	(kg)		(mg)	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
151	10	37.0	1.8	66.6	96	137	77	74	63	67	127	156	102	98	95	97	73	110	60	53	48	51	113	107	110	96	88	86
18	1	12.0	1.8	21.6	69	68	60	55	54	54	79	95	79	81	80	74	64	48	54	45	38	40	166	115	111	104	98	100
110	3	13.2	1.8	23.8	73	77	67	62	57	58	86	99	86	81	82	80	56	59	51	49	48	49	125	117	107	98	100	100
109	2	10.5	1.8	18.9	75	75	75	62	58	54	90	87	99	87	76	78	63	70	63	48	48	40	182	170	122	102	93	102
15	11	31.5	1.8	56.7	91	78	75	71	66	66	122	114	102	102	98	95	78	65	58	56	54	54	105	96	108	100	93	91
132	10	25.8	1.8	46.4	70	65	56	53	52	54	95	92	86	80	77	78	57	50	44	43	43	42	75	90	81	76	74	73
134	9	39.5	1.8	71.1	108	85	80	75	65	65	129	105	108	101	105	98	86	64	57	54	51	51	110	120	100	97	89	93
144	0	10.2	1.8	18.4	127	72	63	64	63	58	145	105	90	90	86	81	113	52	48	45	43	43	197	144	136	131	133	129
11	4	16.7	1.8	30.1	71	60	50	50	50	50	107	98	90	85	83	83	57	55	38	37	36	38	115	•	87	84	83	80
93	11	33.5	1.8	60.3	86	74	67	68	79	75	122	120	105	80	91	97	71	66	54	56	60	51	63	88	76	119	113	91
139	6	20.0	1.8	36.0	80	62	58	62	56	60	112	98	95	90	87	86	55	41	43	45	42	43	96	110	89	84	76	77
101	4	15.8	1.8	28.4	77	61	70	64	62	57	100	91	95	82	83	82	64	46	55	52	49	43	98	78	97	77	78	80
100	5	15.0	1.8	27.0	75	70	65	63	69	61	99	92	88	86	90	90	52	51	51	48	46	42	98	111	102	100	100	100
50	9	27.0	1.8	48.6	71	66	67	63	64	58	105	105	98	95	95	94	53	53	52	47	47	43	72	•	78	75	71	65
45	4	14.5	1.8	26.1	91	54	78	64	60	57	106	67	102	88	83	82	81	47	60	51	48	48	115	88	88	85	84	86
194	3	16.0	1.8	28.8	93	93	65	63	57	58	115	101	96	88	88	83	72	68	50	47	44	45	115	113	104	101	92	91
53	7	24.4	1.8	43.9	81	65	68	65	61	60	106	94	94	91	87	87	67	56	58	55	53	50	80	96	85	81	78	75
52	1	11.0	1.8	19.8	128	61	68	58	53	53	152	108	92	88	80	84	103	50	53	46	39	39	78	125	117	113	113	108
41	11	37.1	1.8	66.8	92	85	71	66	63	62	131	112	105	102	97	93	75	70	57	54	48	46	76	113	66	65	66	59
1	8	22.4	1.8	40.3	75	71	76	57	71	71	100	99	98	76	99	99	60	57	59	51	59	53	94	100	120	108	111	100
31	2	9.7	1.8	17.5	60	57	53	48	46	50	88	100	84	74	74	71	48	42	38	35	36	37	98	110	104	86	87	88
211	6	14.8	1.8	26.6	94	67	60	55	53	55	120	93	92	82	86	82	77	50	46	43	43	41	83	84	83	83	74	72
40	8	24.0	1.8	43.2	80	82	95	73	67	68	112	123	114	106	99	100	62	61	73	55	51	51	76	93	92	85	87	84
206	4	17.2	1.8	31.0	116	87	73	71	65	56	128	113	91	101	95	93	104	68	67	55	49	44	129	100	110	96	94	92
141	1	13.4	2.0	26.8	105	88	67	59	53	57	115	112	99	88	80	86	101	76	51	44	40	42	182	90	141	131	122	127
183	7	21.4	2.0	42.8	82	70	72	62	61	57	108	94	94	93	86	86	64	58	61	48	48	44	100	115	105	91	81	79
103	5	19.0	2.0	38.0	76	72	57	61	57	55	107	109	94	95	90	88	58	51	43	43	40	41	104	125	72	75	69	65
208	2	13.6	2.0	27.2	65	57	50	49	50	49	85	78	76	71	71	73	50	44	39	40	37	39	•	98	92	89	87	86
20	11	37.0	2.0	74.0	65	63	71	60	57	62	93	87	91	84	88	88	56	47	56	43	43	52	70	90	102	78	74	75
62	4	14.7	2.0	29.4	101	80	62	60	58	58	120	115	90	88	90	91	89	59	48	48	46	47	131	104	83	80	78	78
94	6	16.5	2.0	33.0	81	71	80	70	57	58	100	100	•	100	81	74	55	59	•	51	43	43	81	86	88	87	71	71
201	2	13.5	2.0	27.0	117	62	56	56	61	57	135	91	90	87	86	88	93	51	47	45	45	46	78	100	97	96	94	96
97	4	15.0	2.0	30.0	68	65	72	65	62	52	106	103	95	95	92	90	52	56	52	42	39	37	105	110	107	102	94	97
99	3	19.0	2.0	38.0	81	57	58	55	55	54	106	91	93	90	83	83	59	44	44	41	40	39	115	97	88	87	86	83
63	3	13.7	2.0	27.4	85	60	62	63	65	57	108	93	93	86	72	85	68	47	52	49	60	44	104	110	102	92	90	84
107	10	26.3	2.0	52.6	97	76	64	56	57	63	111	107	91	82	86	88	82	53	47	46	45	50	78	65	72	68	68	84
135	7	18.0	2.0	36.0	82	84	62	63	58	53	110	108	97	95	88	86	66	61	51	48	44	43	86	84	87	91	84	82
116	6	19.0	2.0	38.0	121	73	80	63	58	68	129	101	103	93	86	92	95	55	63	52	48	51	84	96	102	89	88	98
133	10	29.0	2.0	58.0	108	114	96	85	81	85	133	136	128	115	111	111	94	100	76	70	66	63	76	104	108	89	87	84
30	10	30.9	2.0	61.8	63	90	84	76	77	92	90	116	114	101	102	128	53	69	68	64	65	71	111	98	100	101	91	131
129	10	33.5	2.0	67.0	83	52	56	54	53	54	113	102	96	87	86	90	63	41	41	40	41	42	89	101	87	78	75	73
33	6	20.7	2.0	41.4	69	77	86	57	59	62	109	105	100	96	90	92	55	62	65	46	44	39	72	84	94	72	70	70
212	1	10.5	2.0	21.0	94	71	66	78	68	66	174	98	82	92	95	97	84	53	53	63	52	50	159	127	125	147	133	129
209	3	16.0	2.0	32.0	85	61	67	61	58	51	145	103	95	87	84	85	72	50	50	47	46	39	104	98	89	86	85	84

CHAPTER 4 : Influence of propofol dose on haemodynamic changes
Systolic, mean and diastolic arterial pressure data (continued)

Patients No	age (yr)	B wt (kg)	Dose group	Propofol dose (mg)	Mean arterial pressure (mmHg) Minutes after induction 0	1	2	3	4	5	Systolic arterial pressure (mmHg) Minutes after induction 0	1	2	3	4	5	Diastolic arterial pressure (mmHg) Minutes after induction 0	1	2	3	4	5	Pulse rate (bpm) Minutes after induction 0	1	2	3	4	5
111	7	24.4	2.0	48.8	75	64	65	65	73	71	116	92	96	98	99	102	51	49	48	48	52	52	75	78	72	74	72	72
113	10	42.0	2.0	84.0	77	82	65	61	67	65	107	102	94	86	91	91	65	61	50	46	49	49	82	98	81	81	82	84
13	8	23.6	2.0	47.2	88	66	66	64	65	64	113	99	97	93	88	92	75	57	53	49	52	50	78	93	75	72	75	75
92	6	18.5	2.0	37.0	64	70	66	50	52	52	96	92	92	82	78	84	53	58	49	40	38	42	91	105	115	91	91	92
160	1	11.0	2.0	22.0	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
55	4	17.0	2.0	34.0	83	78	65	65	58	58	106	100	93	91	88	85	78	65	57	51	47	45	117	122	105	102	97	97
84	11	26.2	2.0	52.4	77	66	70	68	67	67	109	101	103	102	101	101	59	52	52	52	50	52	96	101	93	98	98	92
83	1	10.4	2.0	20.8	85	85	70	66	58	70	94	99	95	93	90	87	66	69	51	47	45	54	127	101	87	78	79	78
165	5	17.0	2.0	34.0	97	73	67	64	62	61	117	106	92	90	85	85	76	60	55	51	48	47	119	107	96	89	86	82
75	2	9.7	2.0	19.4	72	66	61	58	62	58	108	87	89	87	83	88	55	47	37	39	41	39	127	117	115	113	111	115
74	2	11.8	2.0	23.6	77	70	66	63	61	66	104	92	86	88	90	97	64	57	51	49	48	49	110	115	98	100	94	93
177	4	14.0	2.0	28.0	68	55	51	52	47	48	107	97	86	80	79	81	53	42	40	40	35	37	108	101	102	94	86	91
68	1	11.0	2.0	22.0	65	62	55	50	54	48	95	92	86	79	78	78	45	46	37	33	40	34	156	156	141	131	127	127
87	8	27.7	2.0	55.4	73	67	62	61	69	66	94	97	100	92	99	89	57	44	47	54	54	51	117	127	117	107	110	102
70	4	18.0	2.0	36.0	67	70	63	60	56	53	102	111	90	87	85	83	52	53	45	44	44	43	89	92	93	89	87	83
3	8	26.2	2.0	52.4	70	70	74	60	70	64	107	108	104	98	93	94	56	52	52	41	43	40	74	84	97	80	72	75
197	1	8.0	2.0	16.0	91	68	58	53	49	60	123	94	77	73	73	71	71	52	45	43	36	46	192	117	113	107	110	108
181	6	16.6	2.0	33.2	71	57	61	54	53	51	93	86	82	76	73	74	61	45	52	43	42	41	96	97	98	86	86	79
190	7	26.3	2.2	57.9	107	77	75	70	67	65	117	104	102	103	91	95	76	62	54	47	47	46	91	105	93	100	87	86
128	1	11.0	2.2	24.2	97	85	70	63	61	57	108	116	90	86	80	81	75	69	54	48	49	46	144	115	97	96	97	100
5	7	20.0	2.2	44.0	88	75	67	56	53	52	113	105	93	85	81	80	74	59	59	46	43	43	96	100	83	78	78	76
187	6	22.7	2.2	49.9	75	77	63	55	55	55	105	108	95	85	85	81	61	58	50	43	44	42	76	•	90	74	70	68
14	8	46.0	2.2	101.2	107	96	71	63	68	68	138	115	98	114	109	103	82	79	60	68	53	52	91	91	100	97	78	72
175	9	24.0	2.2	52.8	84	60	58	54	52	56	122	117	101	91	86	85	60	47	41	37	36	37	91	91	82	75	72	74
130	7	20.5	2.2	45.1	68	65	76	106	70	66	99	96	101	123	105	102	56	54	64	82	52	53	69	102	93	101	68	70
7	2	11.1	2.2	24.4	72	64	55	52	52	54	100	93	76	76	80	80	60	47	46	41	39	45	136	104	104	100	97	104
198	3	15.0	2.2	33.0	86	61	52	58	62	57	129	110	93	90	91	86	66	44	42	38	46	43	117	94	80	76	75	72
157	2	16.6	2.2	36.5	63	61	57	50	48	49	97	88	84	79	77	71	51	49	44	40	37	37	87	115	88	85	81	89
202	1	10.0	2.2	22.0	80	64	68	61	68	63	105	90	88	91	91	92	59	48	49	44	50	49	150	138	136	136	127	129
155	5	16.8	2.2	37.0	68	72	75	71	64	56	97	86	96	97	91	85	51	62	59	63	53	45	104	141	122	101	93	88
149	11	44.3	2.2	97.5	76	77	67	66	89	63	107	104	98	99	93	90	56	64	51	49	49	49	100	117	80	81	74	72
140	11	23.5	2.2	51.7	72	75	68	68	66	64	101	108	91	98	92	94	62	59	57	57	54	51	70	78	75	75	75	75
184	3	14.2	2.2	31.2	87	65	66	62	56	55	108	90	86	84	80	82	76	53	54	48	46	44	127	72	90	83	80	82
2	9	24.4	2.2	53.7	87	86	70	57	54	53	107	95	88	84	82	78	73	56	56	46	44	43	78	101	81	73	72	70
164	3	13.4	2.2	29.5	82	87	56	62	54	50	106	113	85	77	74	76	66	68	47	49	42	41	83	104	86	88	78	79
188	4	16.9	2.2	37.2	74	71	50	48	49	49	93	99	76	74	73	73	61	55	36	35	36	36	87	84	70	63	63	66
179	4	15.4	2.2	33.9	86	67	56	58	57	56	107	99	92	87	86	86	69	45	40	41	40	38	83	97	91	87	82	91
47	8	29.0	2.2	63.8	76	77	73	70	66	68	112	107	106	100	102	99	64	62	54	52	49	50	80	111	89	80	78	75
66	10	22.0	2.2	48.4	83	93	75	71	91	95	101	114	104	102	111	122	70	67	63	55	78	80	80	110	86	83	108	110
118	1	10.7	2.2	23.5	81	72	63	64	58	55	108	84	79	92	83	80	68	55	55	48	46	44	129	131	119	125	122	117
27	1	10.4	2.2	22.9	92	64	48	52	45	52	105	90	74	75	68	74	68	53	41	40	34	40	187	144	131	129	125	119
58	2	13.8	2.2	30.4	81	82	61	56	53	54	110	104	88	84	87	79	60	58	48	44	44	44	97	108	94	88	85	83
90	5	19.0	2.2	41.8	63	66	61	55	57	54	85	90	83	79	84	79	55	57	50	45	43	44	77	93	86	79	78	78
65	4	17.0	2.2	37.4	84	60	56	51	53	54	104	98	83	83	77	73	61	48	45	42	41	44	94	88	89	85	87	83

CHAPTER 4 : Influence of propofol dose on haemodynamic changes
Systolic, mean and diastolic arterial pressure data (continued)

Patients No	age (yr)	B wt (kg)	Dose group	Propofol dose (mg)	Mean arterial pressure (mmHg) Minutes after induction 0	1	2	3	4	5	Systolic arterial pressure (mmHg) Minutes after induction 0	1	2	3	4	5	Diastolic arterial pressure (mmHg) Minutes after induction 0	1	2	3	4	5	Pulse rate (bpm) Minutes after induction 0	1	2	3	4	5
56	4	13.0	2.2	28.6	70	64	56	54	50	46	102	99	90	79	78	76	56	43	43	41	37	35	105	108	101	77	79	78
32	8	34.0	2.2	74.8	96	68	60	60	61	53	120	98	90	83	90	88	68	52	45	37	38	37	88	81	80	76	77	82
123	7	20.6	2.2	45.3	92	73	60	53	52	52	113	108	95	92	92	85	64	50	43	39	35	34	96	110	87	80	73	75
37	8	30.0	2.2	66.0	82	75	66	70	64	71	111	97	99	98	98	100	67	59	52	55	51	54	113	119	108	102	108	108
91	7	21.2	2.2	46.6	63	54	61	64	63	60	97	87	88	90	91	88	47	38	44	46	46	43	83	98	97	96	91	92
67	2	13.7	2.2	30.1	90	74	62	54	51	49	114	104	92	80	78	74	64	55	49	45	41	39	131	120	108	98	96	100
119	1	8.8	2.2	19.4	95	72	73	74	70	71	106	79	100	95	90	92	81	56	56	56	57	59	166	147	133	127	133	138
39	10	22.4	2.2	49.3	87	67	73	63	61	61	112	101	97	93	83	82	71	51	53	51	45	44	94	110	101	90	92	87
28	2	10.9	2.2	24.0	86	74	60	58	53	50	114	106	86	85	78	75	62	50	46	43	40	38	144	120	111	108	104	101
174	4	16.0	2.4	38.4	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
25	10	26.0	2.4	62.4	86	53	57	51	49	50	117	94	87	82	77	80	66	45	40	36	35	38	102	85	80	72	65	68
71	5	15.0	2.4	36.0	81	65	62	60	57	60	106	97	92	87	86	84	58	55	51	48	45	46	102	117	101	101	98	98
168	1	9.0	2.4	21.6	80	63	73	76	78	75	102	91	96	100	102	107	65	50	55	57	59	56	150	131	144	141	133	141
167	2	11.5	2.4	27.6	102	74	75	65	70	66	131	101	97	90	95	88	74	61	58	50	55	52	131	111	117	92	102	97
77	2	12.6	2.4	30.2	68	60	66	52	57	54	94	83	82	80	86	81	48	44	47	40	43	40	85	96	87	88	88	79
76	2	14.4	2.4	34.6	84	78	72	67	66	68	104	106	101	96	88	97	59	48	48	48	54	44	125	141	125	133	119	119
72	6	19.5	2.4	46.8	86	70	62	62	62	60	112	92	95	87	88	86	68	58	55	48	49	46	113	110	111	97	96	94
9	3	15.8	2.4	37.9	72	74	75	55	55	52	97	96	95	91	78	77	60	63	63	48	43	40	107	105	119	104	85	86
73	2	12.5	2.4	30.0	73	60	56	52	52	50	105	93	86	78	77	77	54	46	41	36	37	35	141	120	110	105	100	101
51	5	21.0	2.4	50.4	71	67	77	64	57	58	103	92	112	92	85	82	52	52	57	46	42	39	77	113	108	90	86	87
192	6	18.7	2.4	44.9	77	73	63	74	88	101	105	99	108	107	129	128	61	54	49	58	61	79	86	100	92	115	104	129
196	6	18.8	2.4	45.1	90	91	82	72	73	65	116	121	110	105	100	100	69	75	62	54	55	48	91	117	102	91	101	84
35	1	11.9	2.4	28.6	92	50	44	52	44	45	103	94	78	74	71	71	89	40	30	39	32	31	138	•	94	89	86	84
200	7	20.5	2.4	49.2	76	75	55	54	54	56	106	104	88	87	82	83	60	58	45	42	39	42	97	104	98	92	89	87
54	2	12.2	2.4	29.3	102	87	67	88	94	90	162	107	103	99	97	93	82	70	62	51	50	50	147	100	96	88	94	90
61	5	17.5	2.4	42.0	91	75	63	56	56	55	114	100	88	85	82	83	68	55	53	48	46	45	85	110	86	80	82	82
182	10	49.6	2.4	119.0	102	84	68	65	73	76	142	134	112	110	97	104	76	60	51	52	57	60	72	102	83	80	84	78
59	7	19.6	2.4	47.0	86	87	68	64	61	56	113	112	94	91	90	87	61	69	54	49	45	41	92	108	101	68	68	83
6	5	18.0	2.4	43.2	90	66	56	49	51	52	110	90	88	83	82	83	63	46	44	40	40	37	100	107	91	75	77	77
186	8	29.0	2.4	69.6	96	70	63	57	57	60	123	97	93	85	86	83	73	53	52	48	45	47	110	119	98	90	88	87
163	4	17.2	2.4	41.3	75	61	63	55	54	54	105	91	88	85	82	81	55	42	43	40	36	38	101	110	102	100	94	94
124	8	26.9	2.4	64.6	75	86	63	58	61	62	129	121	106	109	103	104	55	63	46	45	43	41	86	94	91	91	85	77
146	8	24.0	2.4	57.6	82	65	63	66	65	63	129	96	104	97	98	99	55	45	42	44	42	43	122	96	102	89	83	79
122	7	20.0	2.4	48.0	77	68	64	61	58	62	87	96	94	91	90	88	59	49	47	42	43	44	86	105	82	82	79	78
152	2	13.9	2.4	33.4	58	66	61	55	60	52	121	97	92	91	92	84	50	50	44	39	42	39	153	138	127	115	115	113
150	1	8.1	2.4	19.4	108	67	61	57	55	58	122	90	82	80	77	78	96	54	52	46	47	46	83	102	101	104	98	92
21	9	27.0	2.4	64.8	87	67	71	63	63	67	109	90	97	93	93	92	71	53	57	52	50	53	107	117	102	89	85	82
104	1	9.2	2.4	22.1	109	145	73	72	61	56	123	157	107	94	90	88	83	120	59	51	44	42	72	71	150	150	127	129
112	5	21.4	2.4	51.4	67	76	60	61	50	50	97	104	87	93	80	76	53	57	49	40	35	36	94	104	80	93	73	72
136	12	24.4	2.4	58.6	75	77	67	57	54	63	107	96	105	91	90	94	58	53	46	40	40	45	72	98	74	70	69	74
98	11	28.4	2.4	68.2	84	71	65	61	56	63	122	107	100	98	98	99	69	48	50	43	40	36	76	82	92	84	70	77
12	9	32.7	2.4	78.5	81	91	80	88	109	91	117	116	107	122	147	117	68	72	67	66	86	70	87	93	89	102	125	117
142	1	13.3	2.4	31.9	80	62	56	52	55	52	108	94	87	78	74	75	53	45	43	40	41	40	142	120	119	111	108	110
158	3	19.4	2.4	46.6	139	104	102	85	75	68	159	117	137	101	95	93	108	96	83	68	63	57	141	119	91	100	88	83

CHAPTER 4 : Influence of propofol dose on haemodynamic changes
Systolic, mean and diastolic arterial pressure data (continued)

Patients No	age (yr)	B wt (kg)	Dose group	Propofol dose (mg)	Mean arterial pressure (mmHg) Minutes after induction						Systolic arterial pressure (mmHg) Minutes after induction						Diastolic arterial pressure (mmHg) Minutes after induction						Pulse rate (bpm) Minutes after induction					
					0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
86	6	18.9	2.4	45.4	88	90	71	61	56	55	102	105	92	86	85	77	75	74	49	50	44	41	92	119	111	90	87	84
22	9	23.8	2.4	57.1	92	57	61	52	51	51	126	94	93	86	84	82	68	43	42	38	38	39	94	72	86	72	71	69
161	0	7.8	2.4	18.7	110	80	67	78	67	62	115	107	103	98	94	81	103	74	57	57	52	52	214	178	166	159	163	163
127	1	9.8	2.4	23.5	81	71	62	58	58	48	101	98	78	72	70	79	59	52	48	45	43	42	117	105	105	101	101	102
156	2	12.5	2.4	30.0	121	74	63	57	56	60	145	105	100	95	88	93	94	56	45	44	41	43	133	117	•	87	84	113
154	9	20.0	2.4	48.0	81	82	85	66	74	75	103	102	103	82	94	101	70	65	66	61	65	66	92	104	97	122	110	120
153	3	15.3	2.4	36.7	80	66	70	62	58	62	103	95	92	83	82	82	65	47	56	47	45	49	84	87	108	86	88	85
203	1	9.4	2.6	24.4	81	65	62	57	54	54	129	100	82	81	79	79	58	48	48	45	41	44	166	110	111	108	107	102
34	2	14.8	2.6	38.5	77	73	58	53	53	55	92	85	85	78	79	75	58	62	51	45	42	43	144	136	117	108	108	107
121	1	9.7	2.6	25.2	64	60	61	54	55	56	96	84	85	81	81	82	49	48	48	42	45	46	111	105	110	101	104	101
16	11	31.3	2.6	81.4	84	82	58	60	57	57	116	121	99	95	93	93	62	59	48	42	41	44	82	87	89	86	75	75
117	8	29.0	2.6	75.4	97	74	68	63	70	64	129	105	104	98	101	97	75	56	52	46	53	45	86	113	101	88	102	86
125	1	10.4	2.6	27.0	82	62	58	55	57	63	104	95	91	88	84	90	64	49	42	44	43	46	156	136	120	122	120	119
44	3	17.4	2.6	45.2	108	68	67	68	67	66	117	99	95	91	92	91	97	58	56	56	55	54	120	105	104	107	104	105
214	4	18.0	2.6	46.8	81	87	70	67	67	56	106	115	112	104	93	90	67	61	48	51	48	42	147	88	129	110	85	78
38	9	22.0	2.6	57.2	97	106	88	83	78	80	127	129	116	108	109	111	83	81	65	64	62	63	125	138	127	118	113	115
210	2	10.3	2.6	26.8	127	83	68	61	58	58	158	113	100	95	91	88	94	62	52	47	47	46	166	138	102	102	94	93
36	1	9.0	2.6	23.4	88	63	61	56	52	55	121	88	81	78	78	76	67	53	50	44	42	43	153	131	131	127	122	127
207	2	16.8	2.6	43.7	140	56	61	56	53	50	163	78	76	74	72	70	125	48	48	46	43	44	163	100	105	101	96	100
204	11	34.1	2.6	88.7	101	66	62	58	62	55	117	93	95	94	83	87	80	51	47	43	44	39	70	87	84	75	63	60
205	7	26.2	2.6	68.1	71	70	58	57	58	55	109	96	91	88	91	87	56	56	47	46	43	42	85	115	96	92	84	81
213	8	20.0	2.6	52.0	77	67	55	50	49	50	105	101	94	82	81	79	57	51	40	37	33	35	96	108	88	81	73	77
96	10	30.5	2.6	79.3	108	90	77	71	71	70	136	132	114	108	108	113	77	63	62	60	50	50	101	113	72	68	69	67
8	5	16.4	2.6	42.6	101	80	71	62	60	60	134	106	108	92	95	87	87	60	54	46	46	45	120	104	97	90	86	84
147	8	35.0	2.6	91.0	114	75	70	60	63	63	126	109	92	95	96	96	86	55	59	47	48	36	108	113	91	78	75	74
64	1	11.6	2.6	30.2	84	73	56	63	54	52	110	95	85	84	77	77	70	59	43	47	43	42	101	119	107	100	97	90
169	1	9.9	2.6	25.7	128	83	60	57	56	54	156	113	81	80	76	75	95	64	44	46	50	43	101	166	131	131	131	129
78	8	23.4	2.6	60.8	85	81	67	62	61	62	121	108	100	96	94	94	62	61	48	45	43	43	97	122	97	90	87	85
24	6	34.0	2.6	88.4	83	119	74	66	64	61	112	132	99	102	97	101	76	93	49	47	•	•	86	107	71	61	65	72
80	4	16.0	2.6	41.6	70	74	58	60	56	55	95	95	85	85	81	80	55	68	47	47	46	43	71	100	81	83	79	78
162	4	19.2	2.6	49.9	65	91	78	66	62	61	97	107	113	98	103	99	56	79	55	46	44	42	88	73	97	88	86	84
26	3	13.3	2.6	34.6	84	56	60	53	54	55	122	96	91	83	84	82	67	44	45	43	•	43	150	108	102	104	100	107
193	4	19.6	2.6	51.0	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
48	2	14.7	2.6	38.2	62	73	74	65	76	58	86	90	90	91	92	81	52	54	57	54	54	46	110	96	119	94	105	92
137	6	22.4	2.6	58.2	85	73	68	64	53	63	114	99	91	96	91	94	63	60	51	48	43	44	93	108	122	110	89	84
106	9	26.2	2.6	68.1	68	64	67	65	57	59	109	99	106	95	90	91	52	44	48	46	41	42	68	96	105	86	79	79
145	7	21.8	2.6	56.7	88	64	62	61	54	50	128	98	97	93	86	85	72	54	47	48	40	38	78	90	84	87	80	80
60	4	14.6	2.6	38.0	97	93	87	83	81	76	114	136	104	100	109	98	84	74	67	70	59	58	100	102	81	93	93	100
102	4	19.8	2.6	51.5	77	54	62	64	57	58	103	88	88	92	91	90	57	46	50	48	49	45	107	81	101	97	89	88
57	6	23.4	2.6	60.8	71	62	61	60	60	58	105	100	101	94	94	87	51	47	51	38	43	46	77	96	96	65	68	85

Chapter 5. Comparison of cardiovascular effects of propofol and thiopentone
General data (propofol group)

Patient no	Sex	Group	Age (yr)	Weight (kg)	Height (cm)	Surface area (m2)	Mood	Operation	Drug	Dose	Pain	Apnoea	Apn. duration (sec)
36	M	AP	1.0	10.5	82	0.46	Agi	Orchidopexy	propofol	26.0	N	N	•
37	M	AP	1.0	11.5	86	0.50	Cry	Orchidopexy	propofol	28.7	N	N	•
35	M	AP	0.8	9.4	76	0.42	Cry	Hernia	propofol	24.0	Y	N	•
38	M	AP	1.9	10.7	87	0.50	Agi	Orchidopexy	propofol	27.0	N	Y	•
39	M	AP	1.4	13.5	80	0.50	Cry	Orchidopexy	propofol	33.7	N	Y	•
33	M	AP	1.0	9.3	75	0.41	Calm	Repair anus	propofol	23.0	N	N	•
34	M	AP	1.0	10.9	81	0.46	Agi	Pyeloplasty	propofol	27.5	N	Y	10
41	M	AP	0.9	9.3	72	0.40	Agi	Herniotomy	propofol	23.7	N	Y	45
40	M	AP	2.0	10.2	85	0.47	Calm	Herniotomy	propofol	25.5	Y	Y	60
7	M	BP	11.0	37.1	154	1.28	Calm	Circumcision	propofol	92.0	Y	N	•
12	M	BP	2.4	14.0	90	0.56	Agi, cry	Orchidopexy	propofol	35.0	N	Y	10
10	F	BP	11.0	26.8	143	1.05	Calm	Ex acc auricle	propofol	68.7	N	Y	10
8	F	BP	9.0	32.1	137	1.11	Calm	Herniotomy	propofol	80.0	Y	N	•
9	M	BP	2.5	11.9	95	0.55	Agi,cry	Circumcision	propofol	30.0	N	N	•
6	M	BP	4.0	14.5	109	0.71	Agi,cry	Herniotomy	propofol	36.0	N	Y	60
5	M	BP	4.0	18.8	110	0.80	Calm	Herniotomy	propofol	47.0	N	Y	20
20	M	BP	5.8	13.8	108	0.70	Agi	Ex penile fistula	propofol	33.5	N	N	•
18	M	BP	4.0	16.2	105	0.71	Calm	Circumcision	propofol	40.0	Y	Y	75
19	M	BP	2.0	12.3	90	0.52	Calm	Orchidopexy	propofol	30.0	Y	Y	40
3	M	BP	2.0	12.7	100	0.60	Calm	HLPPV	propofol	32.0	N	Y	•
42	M	BP	5.0	15.0	110	0.72	Calm	Hydrocele	propofol	42.5	N	N	•

Chapter 5. Comparison of cardiovascular effects of propofol and thiopentone
General data (thiopentone group)

Patient no	Sex	Group	Age (yr)	Weight (kg)	Height (cm)	Surface area (m2)	Mood	Operation	Drug	Dose	Pain	Apnoea	Apn. duration (sec)
24	F	AT	0.8	7.6	71	0.33	Agi, cry	Ex skin lesion	Thiopentone	38.0	N	N	•
22	M	AT	1.9	11.3	86	0.50	Calm	Herniotomy	Thiopentone	56.0	N	Y	30
23	M	AT	0.6	8.7	77	0.41	Calm	Herniotomy	Thiopentone	44.0	N	N	•
25	M	AT	1.0	10.7	87	0.50	Agi,cry	Orchdopexy	Thiopentone	51.0	N	N	•
29	M	AT	1.0	10.0	82	0.45	Agi	Orchidopexy	Thiopentone	64.0	N	Y	30
26	M	AT	1.3	8.7	78	0.41	Calm	Orchidopexy	Thiopentone	43.5	N	Y	30
30	M	AT	1.0	8.9	74	0.40	Agi	Explo testes	Thiopentone	45.0	N	Y	20
27	M	AT	1.0	10.0	80	0.43	Agi,slp	Herniotomy	Thiopentone	50.0	N	N	•
28	F	AT	1.0	11.2	89	0.51	Calm	Repair ear	Thiopentone	56.0	N	Y	20
11	M	BT	4.0	19.5	110	0.83	Calm	Herniotomy	Thiopentone	97.5	N	N	•
13	M	BT	2.5	10.7	82	0.46	Calm	Hypospadious	Thiopentone	53.5	N	N	•
4	M	BT	6.0	18.9	118	0.85	Calm	Thy cyst	Thiopentone	95.0	N	Y	30
1	F	BT	2.8	15.0	103	0.66	Calm	Herniotomy	Thiopentone	75.0	N	Y	10
2	M	BT	3.0	16.0	104	0.68	Calm	Orchidopexy	Thiopentone	75.0	N	N	•
17	F	BT	2.8	12.3	92	0.55	Calm	Release tri thuml	Thiopentone	62.0	N	N	•
16	F	BT	11.0	33.2	145	1.16	Agi,cry	Caut wart	Thiopentone	165.0	Y	Y	60
31	M	BT	2.3	8.9	86	0.43	Calm	Penile fistula	Thiopentone	45.0	N	Y	30
21	F	BT	4.3	15.1	102	0.66	Calm	Herniotomy	Thiopentone	75.0	N	Y	55
14	M	BT	5.6	16.0	114	0.80	Calm	Ureter reimpl	Thiopentone	80.0	N	N	•
15	F	BT	3.8	15.0	102	0.66	Calm	Ex cyst	Thiopentone	75.0	N	N	•

Chapter 5: Comparison of cardiovascular effects of propofol and thiopentone
Systolic, mean and diastolic arterial pressure data (propofol group)

Patient no	Group	Systolic arterial pressure (mmHg) minutes after induction						Diastolic arterial pressure (mmHg) minutes after induction						Mean arterial pressure (mmHg) minute after induction						Heart rate (bpm) minute after induction					
		0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
36	AP	111	111	103	96	92	87	86	64	61	53	47	47	95	86	73	72	61	60	153	144	133	133	129	125
37	AP	109	103	93	88	90	83	74	58	55	55	50	51	86	73	68	62	71	63	150	127	120	119	115	113
35	AP	79	104	104	94	93	91	65	58	70	52	56	52	70	75	84	73	68	72	197	153	153	136	141	147
38	AP	97	108	87	85	84	84	53	57	49	45	43	46	73	76	63	60	55	56	92	108	93	89	89	92
39	AP	120	85	67	82	84	82	68	48	45	44	45	44	95	62	55	55	56	55	156	115	113	100	102	105
33	AP	111	117	88	82	84	79	82	76	47	41	38	41	98	87	62	55	52	54	188	178	119	117	111	111
34	AP	129	100	96	91	84	83	82	73	52	49	46	47	92	86	70	63	61	58	182	174	131	131	125	125
41	AP	100	111	103	112	101	106	73	61	50	47	52	45	85	78	68	72	74	62	211	129	141	141	117	115
40	AP	85	98	74	76	74	75	61	49	39	37	34	36	77	67	50	51	48	49	129	117	98	105	105	105
7	BP	113	109	117	113	97	116	70	64	69	58	60	78	87	82	85	76	77	99	82	107	94	88	91	98
12	BP	87	70	91	79	76	74	55	51	55	49	47	44	75	62	75	60	56	55	111	107	119	107	107	102
10	BP	107	123	108	96	87	96	60	73	53	46	46	48	80	104	71	63	60	62	97	95	92	94	98	100
8	BP	108	103	87	88	85	87	61	55	47	48	49	48	82	71	61	61	63	63	68	76	78	80	80	76
9	BP	155	100	95	87	92	84	85	67	54	50	44	38	122	81	75	63	60	52	150	129	147	117	107	104
6	BP	115	102	104	101	101	101	84	68	70	65	57	56	97	77	84	80	72	75	107	122	113	120	115	111
5	BP	99	94	86	83	79	80	57	44	47	46	43	43	76	58	61	61	55	56	98	101	105	102	97	100
20	BP	97	78	74	81	82	80	56	40	41	40	40	41	73	52	50	53	54	54	90	96	87	94	93	93
18	BP	105	96	96	91	80	84	76	58	55	53	48	51	85	73	68	66	60	64	102	120	117	108	104	105
19	BP	104	100	87	81	82	81	72	63	47	44	48	43	83	81	63	55	63	53	105	104	98	102	102	104
3	BP	91	84	79	79	73	74	73	48	50	49	44	43	82	58	60	57	52	53	110	96	102	92	89	87
42	BP	99	83	82	79	75	79	66	48	47	44	44	43	81	60	61	53	54	54	93	74	83	79	77	72

Chapter 5: Comparison of cardiovascular effects of propofol and thiopentone
Systolic, mean and diastolic arterial pressure data (thiopentone group)

Patient no	Group	Systolic arterial pressure (mmHg) minutes after induction						Diastolic arterial pressure (mmHg) minutes after induction						Mean arterial pressure (mmHg) minute after induction						Heart rate (bpm) minute after induction					
		0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
24	AT	121	104	105	98	87	81	78	69	66	57	50	49	98	84	85	73	64	63	192	178	159	156	144	144
22	AT	93	87	88	82	81	80	64	58	50	46	42	46	78	65	63	55	54	56	113	129	113	108	113	113
23	AT	97	109	143	121	129	120	77	73	82	82	85	69	83	90	123	101	118	91	120	125	147	141	147	144
25	AT	109	91	98	97	94	85	85	58	71	62	59	50	101	72	91	75	71	63	145	117	150	125	120	108
29	AT	132	101	102	100	95	91	91	60	56	58	53	54	104	83	78	75	70	74	185	153	150	141	141	136
26	AT	96	126	95	87	84	82	60	90	48	51	45	47	80	109	64	68	60	61	122	150	105	107	107	105
30	AT	117	117	105	101	98	100	73	70	65	64	59	57	95	90	78	81	70	73	166	166	141	136	133	133
27	AT	86	86	86	87	82	79	53	53	50	46	48	47	64	62	62	58	61	57	117	129	122	122	120	122
28	AT	90	84	82	79	78	85	53	52	48	45	44	46	65	65	61	56	57	61	133	127	127	125	125	122
11	BT	88	93	83	86	81	82	55	65	52	53	48	50	66	75	62	62	57	62	97	111	107	104	103	102
13	BT	117	105	101	98	88	92	85	70	62	61	55	52	94	84	77	74	63	66	118	133	125	120	117	119
4	BT	75	86	90	90	86	84	59	40	46	43	48	45	68	58	61	60	63	61	78	100	98	92	93	89
1	BT	97	103	97	97	95	91	55	60	61	56	57	53	71	76	74	68	68	67	104	120	117	113	108	107
2	BT	101	102	100	96	96	95	54	54	51	50	47	50	76	74	67	68	64	67	94	120	102	98	90	91
17	BT	90	90	81	74	72	73	59	59	47	45	37	41	76	72	58	55	50	53	120	107	98	97	86	82
16	BT	103	120	116	134	105	101	61	71	69	67	63	61	81	87	86	88	83	77	101	115	119	115	101	98
31	BT	87	93	90	83	92	91	51	58	56	48	50	51	62	70	66	62	62	65	117	133	127	119	120	115
21	BT	96	100	93	86	81	84	54	54	48	42	42	38	73	70	63	56	54	50	117	119	105	102	101	100
14	BT	88	90	90	88	87	82	61	61	60	57	56	51	72	74	71	68	67	64	94	117	120	104	101	93
15	BT	117	103	104	102	100	95	79	66	58	64	57	55	91	81	76	76	71	71	88	110	110	110	108	101

Chapter 5: Comparison of cardiovascular effects of propofol and thiopentone
Derived haemodynamic parameters (propofol group)

Patient no	Group	Stroke volume (ml. b-1) minute after induction						Cardiac output (l. min-1) minute after induction						Systemic vascular resistance (dynes.sec. cm -5) minute after induction						Stroke volume index (ml.b-1. m-2) minute after induction						Cardiac index (l. min-1.m-2) minute after induction					
		0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
36	AP	12.00	13.00	13.50	12.50	14.00	12.50	1.84	1.87	1.79	1.66	1.81	1.56	4139.43	3675.21	3252.57	3464.66	2702.10	3072.00	26.09	28.26	29.35	27.17	30.44	27.17	3.99	4.07	3.90	3.61	3.93	3.40
37	AP	26.00	27.00	25.00	23.00	25.00	24.00	3.90	3.43	3.00	2.74	2.88	2.71	1764.10	1703.12	1813.33	1812.20	1975.65	1858.41	52.00	54.00	50.00	46.00	50.00	48.00	7.80	6.86	6.00	5.47	5.75	5.42
35	AP	7.10	7.10	9.20	9.20	8.50	8.50	1.40	1.09	1.41	1.25	1.20	1.25	4003.72	5523.34	4774.08	4667.52	4539.01	4609.84	16.91	16.91	21.91	21.91	20.24	20.24	3.33	2.59	3.35	2.98	2.85	2.98
38	AP	23.00	21.00	22.00	23.00	23.00	23.00	2.12	2.27	2.05	2.05	2.05	2.12	2759.92	2680.78	2463.34	2344.90	2149.49	2117.20	46.47	42.42	44.44	46.47	46.47	46.47	4.28	4.58	4.13	4.14	4.14	4.28
39	AP	18.40	19.10	22.60	21.70	24.80	22.60	2.87	2.20	2.55	2.17	2.53	2.37	2647.72	2258.14	1722.92	2027.65	1771.03	1854.19	36.80	38.20	45.20	43.40	49.60	45.20	5.74	4.39	5.11	4.34	5.06	4.75
33	AP	8.50	8.80	11.00	11.00	11.00	12.70	1.60	1.57	1.31	1.29	1.22	1.41	4906.13	4443.31	3789.15	3418.80	3407.04	3064.48	20.99	21.73	27.16	27.16	27.16	31.36	3.95	3.87	3.23	3.18	3.02	3.48
34	AP	14.00	17.00	15.60	17.00	15.00	18.40	2.55	2.96	2.04	2.23	1.88	2.30	2888.54	2325.90	2740.26	2263.13	2602.67	2017.39	30.44	36.96	33.91	36.96	32.61	40.00	5.54	6.43	4.44	4.84	4.08	5.00
41	AP	13.40	16.30	12.70	12.00	12.70	12.00	2.83	2.10	1.79	1.69	1.49	1.38	2405.04	2967.61	3037.92	3404.26	3984.12	3594.20	33.50	40.75	31.75	30.00	31.75	30.00	7.07	5.26	4.48	4.23	3.72	3.45
40	AP	18.00	25.00	26.00	27.00	26.00	23.00	2.32	2.92	2.55	2.83	2.73	2.42	2652.89	1832.48	1569.86	1439.15	1406.59	1623.19	38.46	53.42	55.56	57.69	55.56	49.15	4.96	6.25	5.44	6.06	5.83	5.16
7	BP	57.50	50.50	53.00	55.50	54.00	50.00	4.72	5.40	4.99	4.88	4.91	4.90	1476.14	1214.03	1364.91	1244.88	1253.56	1616.33	44.92	39.45	41.41	43.36	42.19	39.06	3.68	4.22	3.89	3.82	3.84	3.83
12	BP	23.00	21.00	22.00	23.00	27.00	28.00	2.55	2.25	2.62	2.46	2.89	2.86	2350.18	2207.39	2291.83	1950.47	1550.71	1540.62	41.07	37.50	39.29	41.07	48.21	50.00	4.56	4.01	4.68	4.40	5.16	5.10
10	BP	46.00	42.00	43.00	42.00	40.00	43.00	4.46	3.99	3.96	3.95	3.92	4.30	1434.33	2085.21	1435.79	1276.60	1224.49	1153.49	43.81	40.00	40.95	40.00	38.10	40.95	4.25	3.80	3.77	3.76	3.73	4.10
8	BP	53.00	42.00	44.00	42.00	43.00	41.00	3.60	3.19	3.43	3.36	3.44	3.12	1820.20	1779.45	1421.91	1451.38	1465.12	1617.46	47.75	37.84	39.64	37.84	38.74	36.94	3.25	2.88	3.09	3.03	3.10	2.81
9	BP	18.00	16.00	18.00	17.00	22.00	21.00	2.70	2.06	2.65	1.99	2.35	2.18	3614.82	3139.54	2267.57	2533.94	2039.08	1904.76	32.73	29.09	32.73	30.91	40.00	38.18	4.91	3.75	4.81	3.61	4.28	3.97
6	BP	29.00	24.00	24.00	29.00	27.00	31.00	3.10	2.93	2.71	3.48	3.11	3.44	2500.81	2103.83	2477.68	1839.08	1855.07	1743.68	40.85	33.80	33.80	40.85	38.03	43.66	4.37	4.12	3.85	4.90	4.37	4.85
5	BP	36.00	28.00	30.00	29.00	29.00	29.00	3.53	2.83	3.15	2.96	2.81	2.90	1723.36	1640.74	1549.21	1649.76	1564.17	1544.83	45.00	35.00	37.50	36.25	36.25	36.25	4.41	3.54	3.94	3.70	3.52	3.63
20	BP	23.10	21.40	21.90	17.30	19.60	17.90	2.08	2.05	1.90	1.63	1.82	1.66	2809.04	2024.92	2099.41	2607.31	2369.98	2595.06	33.00	30.57	31.29	24.71	28.00	25.57	2.97	2.94	2.72	2.32	2.60	2.38
18	BP	27.80	26.90	27.60	27.80	26.20	28.30	2.84	3.23	3.23	3.00	2.72	2.97	2398.08	1809.17	1684.63	1758.59	1761.60	1723.04	39.16	37.99	38.87	39.16	36.90	39.86	3.99	4.55	4.55	4.29	3.84	4.19
19	BP	22.00	18.40	19.10	20.50	18.40	21.20	2.31	1.91	1.87	2.09	1.88	2.20	2874.46	3386.29	2692.60	2104.26	2658.42	1923.08	42.47	35.52	36.87	39.58	35.52	40.93	4.46	3.69	3.61	4.04	3.62	4.26
3	BP	21.00	31.00	31.00	31.00	33.00	31.00	3.41	2.98	3.06	2.85	2.94	2.70	1923.75	1559.14	1568.63	1598.88	1416.41	1572.12	51.67	51.67	50.00	51.67	55.00	51.67	5.68	4.96	5.10	4.75	4.90	4.50
42	BP	27.20	22.50	18.50	19.10	19.60	20.80	2.53	1.66	1.53	1.51	1.51	1.50	2561.67	2886.88	3178.12	2809.99	2862.44	2884.62	37.94	31.38	25.80	26.64	27.34	29.01	3.53	2.32	2.14	2.10	2.11	2.09

Chapter 5: Comparison of cardiovascular effects of propofol and thiopentone
Derived haemodynamic parameters (thiopentone group)

Patient no	Group	Stroke volume (ml. b-1) minute after induction						Cardiac output (l. min-1) minute after induction						Systemic vascular resistance (dynes.sec. cm -5) minute after induction						Stroke volume index (ml.b-1. m-2) minute after induction						Cardiac index (l. min-1.m-2) minute after induction					
		0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
24	AT	10.60	9.90	9.90	11.30	11.30	10.60	2.04	1.76	1.57	1.76	1.63	1.53	3852.20	3813.42	4319.93	3312.91	3146.51	3301.89	31.93	29.82	29.82	34.04	34.04	31.93	6.13	5.31	4.74	5.31	4.90	4.60
22	AT	21.00	20.00	20.00	22.00	20.00	18.00	2.37	2.58	2.26	2.38	2.26	2.03	2629.59	2015.04	2230.09	1851.85	1911.50	2202.56	42.00	40.00	40.00	44.00	40.00	36.00	4.75	5.16	4.52	4.75	4.52	4.07
23	AT	15.00	15.00	19.00	16.00	15.00	14.00	1.80	1.88	2.79	2.26	2.20	2.02	3688.89	3840.00	3523.09	3581.56	4281.18	3611.11	37.04	37.04	46.91	39.51	37.04	34.57	4.44	4.63	6.90	5.57	5.44	4.98
25	AT	12.00	11.50	14.00	13.30	11.50	12.10	1.74	1.35	2.10	1.66	1.38	1.31	4643.68	4280.94	3466.67	3609.02	4115.94	3856.75	24.24	23.23	28.28	26.87	23.23	24.44	3.52	2.72	4.24	3.36	2.79	2.64
29	AT	11.40	15.00	14.70	13.50	13.50	14.00	2.11	2.30	2.20	1.90	1.90	1.90	3945.00	2893.25	2829.93	3152.09	2941.95	3109.24	25.33	33.33	32.67	30.00	30.00	31.31	4.69	5.10	4.90	4.23	4.23	4.23
26	AT	12.70	12.00	12.70	12.00	12.70	12.00	1.55	1.80	1.33	1.28	1.36	1.26	4130.63	4844.44	3839.52	4236.76	35352.27	3873.02	30.98	29.27	30.98	9.27	30.98	29.27	3.78	4.39	3.25	3.13	3.31	3.07
30	AT	19.00	21.00	20.00	22.00	23.00	23.00	3.15	3.49	2.82	2.99	3.06	3.06	2409.64	2065.40	2212.77	2165.78	1830.66	1909.12	47.50	52.50	50.00	55.00	57.50	57.50	7.89	8.72	7.05	7.85	7.65	7.65
27	AT	13.00	16.00	20.00	16.00	19.00	20.00	1.52	2.06	2.44	1.95	2.28	2.44	3366.21	2403.10	2032.79	2377.05	2140.35	1868.85	30.59	37.65	47.06	37.65	44.71	47.06	3.58	4.86	5.74	4.59	5.37	5.74
28	AT	19.00	18.00	17.50	16.00	16.00	19.00	2.53	2.29	2.22	2.00	2.00	2.32	2057.78	2274.72	2195.73	2240.00	2280.00	2120.26	37.26	35.29	34.31	31.37	31.37	37.26	4.96	4.48	4.36	3.92	3.92	4.55
11	BT	44.00	33.00	31.00	36.00	34.00	33.00	4.57	3.66	3.32	3.74	3.50	3.37	1237.11	1638.00	1495.33	1324.79	1302.11	1473.56	53.33	40.00	37.58	43.64	41.21	40.00	5.17	4.44	4.02	4.54	4.25	4.08
13	BT	15.60	16.70	16.70	15.00	15.00	13.30	1.84	2.21	2.09	1.80	1.75	1.58	4085.18	3025.53	2950.90	3288.89	2871.80	3336.07	33.91	36.30	36.30	32.61	32.61	28.91	4.00	4.83	4.54	3.81	3.82	3.44
4	BT	54.00	40.00	42.00	•	46.00	50.00	4.21	4.00	4.12	•	4.28	4.45	1291.55	1160.00	1185.62	•	1178.12	1096.63	63.53	47.06	49.41	•	54.12	58.85	4.96	4.71	4.84	•	5.03	5.24
1	BT	19.10	14.10	14.80	16.20	16.90	16.20	1.99	1.69	1.73	1.83	1.83	1.73	2859.44	3593.38	3418.80	2971.70	2980.50	3092.19	28.94	21.36	22.42	24.55	25.61	24.55	3.01	2.56	2.62	2.77	2.77	2.63
2	BT	32.00	33.00	33.00	36.00	38.00	33.00	3.01	3.96	3.37	3.53	3.42	3.00	2021.28	1494.95	1592.40	1541.95	1497.07	1784.89	47.06	48.53	48.53	52.94	55.88	48.53	4.42	5.82	4.95	5.19	5.03	4.42
17	BT	18.00	18.00	17.00	20.00	23.00	21.00	2.16	1.93	1.67	1.94	1.98	1.72	2814.82	2990.65	2785.11	2268.04	2022.25	2462.25	32.73	32.73	30.91	36.36	41.82	38.18	3.93	3.50	3.03	3.53	3.60	3.13
16	BT	51.00	38.50	32.00	31.00	33.50	39.50	5.15	4.43	3.81	3.57	3.38	3.87	1258.01	1571.99	1806.72	1974.76	1962.47	1591.32	43.97	33.19	27.59	26.72	28.88	34.05	4.44	3.82	3.28	3.07	2.92	3.34
31	BT	24.80	21.40	26.00	23.10	23.70	24.20	2.90	2.85	3.30	2.75	2.84	2.78	1709.40	1967.54	1599.03	1804.36	1744.02	1868.49	57.67	49.77	60.47	53.72	55.12	56.28	6.75	6.62	7.68	6.39	6.61	6.47
21	BT	20.20	19.10	21.90	19.60	21.40	22.50	2.36	2.27	2.30	1.99	2.16	2.25	2471.02	2463.81	2191.78	2240.90	1998.71	1777.78	30.61	28.94	33.18	29.70	32.42	34.09	3.58	3.44	3.48	3.03	3.28	3.41
14	BT	42.00	31.00	30.50	33.50	38.50	37.50	3.95	3.63	3.66	3.45	3.89	3.49	1458.97	1632.20	1551.91	1561.42	1378.42	1468.10	52.50	38.75	38.13	41.88	48.13	46.88	4.94	4.53	4.58	4.36	4.86	4.36
15	BT	39.00	27.00	29.00	31.00	35.00	35.00	3.43	2.97	3.19	3.41	3.78	3.54	2121.21	2181.82	1905.96	1782.99	1502.65	1606.79	59.09	40.91	43.94	46.97	53.03	53.03	5.20	4.50	4.83	5.17	5.73	5.36

Venous concentrations of propofol (ng/ml) at time intervals (min) after bolus dose

	2	3	4	4.5	5	6	6.5	10	15	19	30	45	60	120	240	360	480	720
Patient																		
LWY	2332.10		1506.00			1201.81		650.09	509.37		342.05	200.41	156.44	49.77	12.30	33.81	0.00	0.00
YTH	2208.23		2034.10			1326.48		697.72	714.71		696.18	256.54	197.96	98.72	39.24	31.60	0.00	0.00
TYK	2504.32		1919.85			1371.40		927.85	678.07		347.89	253.10	191.82	47.62		0.00	0.00	0.00
LCF	3720.83			2675.97			2143.39	1507.14		1015.90	524.15	369.00	309.42	100.19	47.33	29.36	6.38	13.86
WKP	3401.13		3126.61			2953.10		904.14	369.30		352.18		305.57		77.17	51.64	23.77	19.72
TPW		5909.89		2194.04			1733.71	1659.52		907.04	575.05	301.23	275.79	132.11	62.45	18.24	24.21	
CCW	2430.93		1568.80			1459.68		764.18	573.79		427.20	573.17	378.65	159.01	33.70	30.63	10.47	11.09
TCY	2478.00		1862.55			1520.99		1111.86	680.09		211.51	182.37	179.24	39.46	10.16	6.90	0.00	0.00
CCH	1458.56		1210.56			865.61		541.14	326.10		132.12	138.54	155.30	32.26	16.31	8.60	0.00	0.00
AYY		3658.94			2711.21	2379.80		1402.04	775.96		338.82	273.79	138.35	53.66	19.03	2.44	0.00	0.00
LCL	2541.62		1642.52			744.71		463.36	321.92		167.76	123.08	83.07	125.27	90.19	51.16	30.50	16.50
YKN	2256.40		1673.45			1295.20		621.50	443.30		173.05	208.50	198.55	68.20	24.35	6.90	5.20	0.00
NSK	2224.59		1742.54			1012.36		539.67	412.31		357.19	205.57	117.95	191.04	152.70	100.87	91.28	0.00
CKS	2153.48		1478.99			1052.58		588.57	392.29		135.37	109.18	50.71	25.27	7.84	1.34	0.00	0.00
LHL	2873.32		1806.02			1379.46		1026.96	617.31		307.29	230.35	129.90	78.11		12.94	5.72	0.00
LKS	2433.48		1569.93			1266.41		1132.91	625.29		381.08	380.18	198.69	104.45	34.98	22.27	18.84	12.37
YKW	1624.55		1181.32			796.27		534.64	320.07		171.60	189.04	98.84	31.73	5.33	3.21	3.54	0.00
TYH	1793.56		1493.21			992.11		346.06	329.08			202.35	156.68	19.48	6.39	4.23	3.41	0.00
LHI		1795.30			1063.02	815.90		559.99	487.43		257.47		138.82	120.79	51.78	23.78	23.52	0.00
TFL	2945.43		1737.30			1141.03		556.22	391.89		193.29	193.68	208.48	32.01	31.70	14.09	2.43	0.00
WKH	2743.33		1343.74			933.45		417.99	350.84		306.70	291.80	147.20	50.33	9.88	5.14	3.76	
NQD		1894.68	873.69			863.66		649.82	587.53		438.87	291.26	172.92	90.64	63.58	62.72	43.06	0.00
YHM	2506.94					1046.14			393.06	410.26	367.16	324.60	274.77	32.58	12.11	7.68	0.00	0.00

Chapter 6: Single dose pharmacokinetics Protein concentration and binding data

Patient	Sex	Age (yr)	Group	Weight (kg)	Total protein (g.l-1)	Albumin (g.l-1)	Propofol protein binding (%)	Free propofol (%)	Alpha 1 acid glycoprotein (mg.l-1)
CHK	M	1.0	<3 yr	11.8	74	45	98.78	1.22	700
LKS	M	1.0	<3 yr	10.9	77	47	99.21	0.79	780
WCK	M	1.3	<3 yr	11.8	78	50	99.01	0.99	380
LWM	M	1.7	<3 yr	11.7	68	46	98.68	1.32	570
WFM	M	2.0	<3 yr	12.5	76	47	98.34	1.66	500
LCK	M	2.0	<3 yr	12.4	70	49	99.05	0.95	500
NTT	F	2.0	<3 yr	9.9	74	44	98.54	1.46	790
CKL	M	2.2	<3 yr	13.9	69	47	98.24	1.76	520
SSM	M	2.9	<3 yr	14.6	75	50	99.10	0.90	440
YTW	M	3.0	<3 yr	14.5	66	46	98.85	1.15	460
NYT	M	3.0	<3 yr	13.4	51	73	98.69	1.31	410
LCP	M	3.0	<3 yr	16.7	66	45	98.76	1.24	380
CKF	M	3.5	3-12yr	12.9	68	43	98.83	1.17	730
LCY	F	3.5	3-12yr	15.2	66	46	98.98	1.02	380
YMF	M	4.2	3-12yr	15.7	69	44	97.90	2.10	570
TKC	M	8.0	3-12yr	27.0	82	45	98.87	1.13	610
WKY	F	10.0	3-12yr	31.2	74	44	99.07	0.93	350
LCS	M	11.0	3-12yr	39.5	67	41	98.95	1.05	410
LCY	M	11.0	3-12yr	50.9	79	49	98.13	1.87	570
CKH	M	11.0	3-12yr	36.0	•	•	98.14	1.86	540
NVT	M	12.0	3-12yr	30.0	70	50	98.59	1.41	490
CKH	M	12.0	3-12yr	38.0	72	45	98.66	1.34	490
YMW	M	21.0	ad	64.0	76	47	98.07	1.93	520
LCK	M	25.0	ad	72.0	73	44	98.31	1.69	790
CLC	M	26.0	ad	64.0	78	43	98.40	1.60	690
LYC	M	27.0	ad	62.0	78	47	98.18	1.82	530
SCY	M	28.0	ad	70.0	72	44	98.38	1.62	730
CCF	M	31.0	ad	66.0	70	42	98.82	1.18	330
KK	M	32.0	ad	64.0	71	41	98.37	1.63	1380
IPS	M	35.0	ad	95.0	81	48	99.35	0.65	520
LCH	M	37.0	ad	62.0	75	43	98.33	1.67	530
LWW	M	30.0	ad	77.0	81	48	98.81	1.19	800
LWY	M	34.0	ad	66.0	71	44	97.78	2.22	500

Chapter 7: Pharmacokinetic model controlled infusion of propofol

Individual patient data (part I study)

P(m)= propofol conc measured, P(p)= propofol conc predicted, Pred er% = prediction error%, Abs pred er% = absolute prediction error%

Patient	Age (yr)	Wt (kg)	Time (min)	P (m) µg.ml-1	P(p) µg.ml-1	Pred er %	Abs pred er%
1	4	17.1	10	7.46	7.50	-0.59	0.59
			18	9.03	10.00	-9.66	9.66
2	4	18.7	10	6.57	10.00	-34.26	34.26
			20	8.22	10.00	-17.76	17.76
			34	8.37	7.93	5.51	5.51
			44	6.53	10.00	-34.72	34.72
			51	4.00	6.12	-34.70	34.70
			70	2.48	2.70	-8.07	8.07
			148	0.55	2.01	-72.61	72.61
3	6	16.2	4	9.62	12.00	-19.80	19.80
			12	10.57	10.97	-3.66	3.66
			20	13.29	14.00	-5.05	5.05
			28	12.34	12.00	2.88	2.88
			32	4.88	4.56	7.01	7.01
			42	2.67	2.55	4.66	4.66
			66	11.56	11.85	-2.50	2.50
4	6	21.8	6	7.85	13.00	-39.65	39.65
			15	11.02	13.00	-15.21	15.21
			26	10.10	9.00	12.19	12.19
			37	9.03	7.00	29.04	29.04
			54	3.98	3.08	29.45	29.45
			72	2.63	2.18	20.59	20.59
			82	0.94	0.96	-2.40	2.40
5	7	19.1	6	6.97	12.00	-41.92	41.92
			11	5.78	10.00	-42.16	42.16
			19	4.57	8.00	-42.81	42.81
			28	4.39	6.00	-26.89	26.89
			35	2.37	3.25	-26.99	26.99
			44	1.40	2.27	-38.28	38.28
			62	0.83	1.61	-48.45	48.45
6	5	16.9	5	6.30	13.00	-51.57	51.57
			13	9.03	13.00	-30.55	30.55
			19	5.95	9.00	-33.90	33.90
			29	5.15	7.00	-26.48	26.48
			43	3.47	5.00	-30.63	30.63
			56	2.66	2.65	0.26	0.26
			71	1.49	1.96	-24.13	24.13
			90	0.82	1.46	-43.87	43.87
7	7	17.3	3	10.14	12.00	-15.54	15.54
			10	9.25	12.00	-22.88	22.88
			15	8.16	10.00	-18.37	18.37
			23	3.75	4.28	-12.43	12.43
			32	2.36	2.37	-0.59	0.59
			46	1.52	1.70	-10.86	10.86
			68	1.41	1.19	18.82	18.82
8	4	15.2	3	4.13	11.00	-62.48	62.48
			11	6.35	11.00	-42.30	42.30
			18	6.83	9.00	-24.14	24.14
			26	5.09	7.00	-27.31	27.31
			32	2.38	4.32	-44.87	44.87
			52	1.22	1.93	-36.61	36.61
			66	0.75	1.53	-50.65	50.65
9	5	18.7	6	6.37	10.00	-36.31	36.31
			10	5.62	10.00	-43.81	43.81
			18	5.02	8.00	-37.25	37.25
			23	3.78	6.00	-37.03	37.03
			28	2.74	4.00	-31.58	31.58
			36	1.93	2.32	-16.85	16.85
			49	1.40	1.63	-14.31	14.31
			64	1.01	1.27	-20.22	20.22
10	6	21.5	5	10.39	11.00	-5.51	5.51
			10	10.72	11.00	-2.52	2.52
			16	9.90	9.00	10.00	10.00
			20	7.52	7.00	7.36	7.36
			25	4.68	3.85	21.42	21.42
			36	2.09	2.08	0.53	0.53
			51	2.16	1.53	41.68	41.68

Chapter 7: Pharmacokinetic model controlled infusion of propofol Individual patient data (part II study).

P(m) Propofol concentration measured, P(p) propofol concentration predicted, Pred er% = prediction error%, Abs pred er% = absolute prediction error%

No	Patient	Age (yr)	Weight (kg)	Infusion duration (min)	Time (sampling) (min after ind)	Phase (maint/ rec)	P(m) (µg.ml-1)	P(p) (µg.ml-1)	Pred er%	Abs pred er%	Individual bias %	Individual prec %	Pred conc (awake) (µg.ml-1)
1	LPK	4	16.7	18	6	Maint	9.82	8.00	22.74	22.74	3.94	3.94	0.83
					10	Maint	10.22	9.00	13.58	13.58	-5.22	5.22	
					16	Maint	9.75	8.11	20.18	20.18	1.38	1.38	
					21	Rec	5.36	5.70	-6.01	6.01			
					31	Rec	2.08	3.28	-36.60	36.60			
					76	Rec	0.72	0.72	-0.26	0.26			
2	CTW	6	20.3	26	9	Maint	9.18	10.00	-8.18	8.18	-14.78	14.78	1.04
					18	Maint	9.77	10.00	-2.29	2.29	-8.89	8.89	
					25	Maint	5.44	6.00	-9.37	9.37	-15.97	15.97	
					48	Rec	1.64	2.15	-24.02	24.02			
3	CWS	9	33.0	47	10	Maint	11.18	10.00	11.84	11.84	1.84	1.84	0.88
					15	Maint	7.87	8.00	-1.58	1.58	-11.58	11.58	
					20	Maint	5.71	7.00	-18.39	18.39	-28.39	28.39	
					25	Maint	6.94	6.00	15.62	15.62	5.62	5.62	
					30	Maint	6.65	6.00	10.84	10.84	0.84	0.84	
					35	Maint	4.77	5.00	-4.57	4.57	-14.57	14.57	
					40	Maint	6.82	5.00	36.42	36.42	26.42	26.42	
					45	Maint	6.49	5.00	29.73	29.73	19.73	19.73	
					49	Rec	3.72	4.10	-9.29	9.29			
					58	Rec	2.67	2.47	8.31	8.31			
					82	Rec	2.51	1.13	121.36	121.36			
4	LKS	10	25.0	56	6	Maint	8.45	10.00	-15.49	15.49	-19.59	19.59	0.86
					10	Maint	10.80	10.00	7.95	7.95	3.85	3.85	
					20	Maint	11.54	9.00	28.23	28.23	24.13	24.13	
					25	Maint	10.40	9.00	15.53	15.53	11.43	11.43	
					30	Maint	8.14	8.00	1.79	1.79	-2.31	2.31	
					38	Maint	8.72	8.00	8.96	8.96	4.86	4.86	
					48	Maint	7.10	7.00	1.46	1.46	-2.64	2.64	
					53	Maint	5.06	6.00	-15.73	15.73	-19.83	19.83	
					58	Rec	4.99	5.00	-0.30	0.30			
					72	Rec	3.27	2.71	20.66	20.66			
					88	Rec	2.27	1.65	37.85	37.85			
					103	Rec	2.49	1.14	118.71	118.71			
5	KHL	8	18.8	20	10	Maint	11.44	10.00	14.37	14.37	1.57	1.57	0.59
					15	Maint	9.75	9.00	8.28	8.28	-4.52	4.52	
					19	Maint	9.25	8.00	15.64	15.64	2.84	2.84	
					32	Rec	4.01	3.75	6.94	6.94			
					58	Rec	1.62	1.40	15.20	15.20			
					71	Rec	1.54	0.95	62.20	62.20			
					82	Rec	1.12	0.72	55.48	55.48			
					101	Rec	0.60	0.50	20.77	20.77			
6	SWF	5	18.8	36	10	Maint	9.11	10.00	-8.86	8.86	-2.16	2.16	0.93
					18	Maint	10.96	11.00	-0.38	0.38	6.32	6.32	
					22	Maint	11.21	11.00	1.94	1.94	8.64	8.64	
					27	Maint	8.65	10.00	-13.50	13.50	-6.80	6.80	
					31	Maint	8.17	9.00	-9.28	9.28	-2.58	2.58	
					35	Maint	6.44	8.00	-19.51	19.51	-12.81	12.81	
					42	Rec	1.50	5.05	-70.35	70.35			
					60	Rec	1.82	2.52	-27.68	27.68			
					89	Rec	0.99	1.10	-9.94	9.94			
					112	Rec	0.87	0.73	20.17	20.17			
7	CPK	6	17.1	23	5	Maint	10.98	10.00	9.78	9.78	10.08	10.08	0.86
					10	Maint	9.96	10.00	-0.46	0.46	-0.16	0.16	
					17	Maint	8.02	8.00	0.24	0.24	0.54	0.54	
					20	Maint	6.02	6.74	-10.73	10.73	-10.43	10.43	
					25	Rec	4.60	5.38	-14.48	14.48			
					30	Rec	2.95	3.91	-24.52	24.52			
					36	Rec	2.39	3.00	-20.29	20.29			
					45	Rec	1.94	2.13	-8.87	8.87			
					61	Rec	1.52	1.25	21.72	21.72			

Chapter 7: Pharmacokinetic model controlled infusion of propofol Individual patient data (part II study) (continued)

P(m) Propofol concentration measured, P(p) propofol concentration predicted, Pred er% = prediction error%, Abs pred er% = absolute prediction error%

No	Patient	Age (yr)	Weight (kg)	Infusion duration (min)	Time (sampling) (min after ind)	Phase (maint/ rec)	P(m) (µg.ml-1)	P(p) (µg.ml-1)	Pred er%	Abs pred er%	Individual bias %	Individual prec %	Pred conc (awake) (µg.ml-1)
8	LHC	6	19.4	35	9	Maint	11.57	8.00	44.63	44.63	14.43	14.43	0.90
					16	Maint	10.69	8.00	33.62	33.62	3.42	3.42	
					20	Maint	9.32	7.00	33.18	33.18	2.98	2.98	
					26	Maint	6.57	6.00	9.56	9.56	-20.64	20.64	
					30	Maint	8.94	6.00	48.95	48.95	18.75	18.75	
					35	Maint	5.56	5.00	11.28	11.28	-18.92	18.92	
					42	Rec	3.06	3.07	-0.17	0.17			
					56	Rec	1.73	1.80	-4.16	4.16			
					69	Rec	1.64	1.18	38.23	38.23			
					81	Rec	1.01	0.85	18.48	18.48			
9	LKH	6	24.5	23	5	Maint	9.11	8.00	13.88	13.88	21.68	21.68	1.45
					10	Maint	6.91	7.00	-1.23	1.23	6.57	6.57	
					15	Maint	4.23	4.66	-9.36	9.36	-1.56	1.56	
					19	Maint	2.17	3.30	-34.36	34.36	-26.56	26.56	
					24	Rec	1.62	2.54	-36.13	36.13			
					31	Rec	1.22	1.89	-35.24	35.24			
					41	Rec	1.15	1.30	-11.52	11.52			
					62	Rec	0.54	0.65	-17.28	17.28			
					86	Rec	0.28	0.36	-23.50	23.50			
10	STK	4	16.5	23	5	Maint	8.72	8.00	9.04	9.04	-5.41	5.41	0.72
					12	Maint	9.35	6.86	36.35	36.35	21.90	21.90	
					15	Maint	7.30	6.00	21.62	21.62	7.17	7.17	
					21	Maint	4.54	5.00	-9.17	9.17	-23.62	23.62	
					25	Rec	3.75	3.39	10.81	10.81			
					32	Rec	2.35	2.42	-2.79	2.79			
					45	Rec	1.18	1.52	-22.28	22.28			
					64	Rec	2.28	0.84	171.82	171.82			
11	KCH	9	29.7	19	6	Maint	9.88	8.00	23.47	23.47	6.37	6.37	0.74
					10	Maint	9.06	8.00	13.22	13.22	-3.88	3.88	
					16	Maint	8.03	7.00	14.74	14.74	-2.36	2.36	
					20	Rec	4.13	4.97	-16.82	16.82			
					25	Rec	3.10	3.48	-10.77	10.77			
					34	Rec	1.76	2.34	-24.59	24.59			
					46	Rec	1.24	1.49	-16.94	16.94			
					66	Rec	0.90	0.78	14.91	14.91			
12	HWL	4	15.3	24	5	Maint	8.80	8.00	10.01	10.01	29.55	29.55	1.25
					10	Maint	5.65	6.00	-5.92	5.92	13.62	13.62	
					15	Maint	3.21	4.00	-19.75	19.75	-0.21	0.21	
					20	Maint	1.99	3.00	-33.73	33.73	-14.19	14.19	
					24	Maint	1.55	3.00	-48.41	48.41	-28.87	28.87	
13	LK	9	23.3	33	5	Maint	6.89	8.00	-13.94	13.94	-2.24	2.24	0.73
					10	Maint	7.80	8.00	-2.53	2.53	9.17	9.17	
					15	Maint	8.32	8.00	3.94	3.94	15.64	15.64	
					20	Maint	6.01	6.25	-3.79	3.79	7.91	7.91	
					26	Maint	4.25	5.23	-18.78	18.78	-7.08	7.08	
					30	Maint	3.26	5.00	-34.89	34.89	-23.19	23.19	
					35	Rec	2.17	3.54	-38.83	38.83			
					44	Rec	1.71	2.53	-32.44	32.44			
					53	Rec	1.29	1.81	-28.47	28.47			
					67	Rec	1.05	1.14	-7.57	7.57			
14	CMF	10	27.0	25	8	Maint	9.04	8.00	12.99	12.99	24.09	24.09	0.69
					13	Maint	11.11	8.00	38.91	38.91	50.01	50.01	
					16	Maint	4.35	6.00	-27.44	27.44	-16.34	16.34	
					20	Maint	3.12	4.80	-34.96	34.96	-23.86	23.86	
					24	Maint	1.96	3.57	-45.11	45.11	-34.01	34.01	
					34	Rec	1.22	2.39	-48.96	48.96			
					44	Rec	1.04	1.64	-36.60	36.60			
					54	Rec	0.82	1.15	-29.18	29.18			

Chapter 7: Pharmacokinetic model controlled infusion of propofol Individual patient data (part II study) (continued)

P(m) Propofol concentration measured, P(p) propofol concentration predicted, Pred er% = prediction error%, Abs pred er% = absolute prediction error%

No	Patient	Age (yr)	Weight (kg)	Infusion duration (min)	Time (sampling) (min after ind)	Phase (maint/ rec)	P(m) (µg.ml-1)	P(p) (µg.ml-1)	Pred er%	Abs pred er%	Individual bias %	Individual prec %	Pred conc (awake) (µg.ml-1)
15	CKK	9	43.7	52	7	Maint	7.95	6.00	32.52	32.52	-6.28	6.28	0.73
					11	Maint	9.66	6.00	60.99	60.99	22.19	22.19	
					15	Maint	8.15	5.00	62.99	62.99	24.19	24.19	
					21	Maint	6.19	4.00	54.76	54.76	15.96	15.96	
					28	Maint	5.65	4.00	41.18	41.18	2.38	2.38	
					35	Maint	3.37	3.50	-3.86	3.86	-42.66	42.66	
					39	Maint	5.73	3.50	63.58	63.58	24.78	24.78	
					44	Maint	3.64	3.00	21.38	21.38	-17.42	17.42	
					51	Maint	2.88	2.50	15.36	15.36	-23.44	23.44	
					57	Rec	2.36	1.80	31.29	31.29			
					82	Rec	1.12	0.73	53.65	53.65			
					108	Rec	0.72	0.41	75.47	75.47			
16	LYS	4	16.3	40	7	Maint	5.90	8.00	-26.21	26.21	8.09	8.09	0.78
					11	Maint	5.59	8.00	-30.15	30.15	4.15	4.15	
					16	Maint	6.15	8.00	-23.15	23.15	11.15	11.15	
					21	Maint	4.56	6.00	-24.05	24.05	10.25	10.25	
					25	Maint	3.64	6.00	-39.35	39.35	-5.05	5.05	
					31	Maint	2.85	5.00	-42.97	42.97	-8.67	8.67	
					36	Maint	1.60	3.50	-54.18	54.18	-19.88	19.88	
					43	Rec	2.22	2.79	-20.27	20.27			
					55	Rec	1.50	1.74	-13.86	13.86			
17	LHY	5	19.6	29	5	Maint	8.60	8.00	7.46	7.46	1.76	1.76	0.86
					11	Maint	9.26	8.00	15.71	15.71	10.01	10.01	
					15	Maint	6.73	6.00	12.23	12.23	6.53	6.53	
					20	Maint	4.00	4.00	0.03	0.03	-5.68	5.68	
					25	Maint	4.57	5.00	-8.58	-8.58	-14.28	14.28	
					29	Maint	5.35	5.00	7.08	7.08	1.38	1.38	
					36	Rec	2.14	2.78	-23.08	23.08			
					41	Rec	2.21	2.23	-0.59	0.59			
					55	Rec	1.30	1.33	-2.09	2.09			
					58	Rec	1.29	1.21	7.24	7.24			
18	PKS	6	23.6	24	6	Maint	5.57	8.00	-30.33	30.33	-44.63	44.63	0.39
					10	Maint	10.59	8.00	32.31	32.31	18.01	18.01	
					16	Maint	8.16	6.00	36.05	36.05	21.75	21.75	
					20	Maint	5.66	4.63	22.18	22.18	7.88	7.88	
					24	Maint	3.71	3.34	11.23	11.23	-3.07	3.07	
					37	Rec	1.83	1.72	6.75	6.75			
					47	Rec	1.25	1.20	4.39	4.39			
					59	Rec	1.24	0.90	38.11	38.11			
19	WKM	9	39.0	41	5	Maint	8.51	6.00	41.82	41.82	12.12	12.12	1.21
					10	Maint	9.49	6.00	58.17	58.17	28.47	28.47	
					15	Maint	9.08	6.00	51.39	51.39	21.69	21.69	
					20	Maint	3.17	4.00	-20.88	20.88	-50.58	50.58	
					25	Maint	4.42	4.00	10.41	10.41	-19.29	19.29	
					35	Maint	5.17	4.00	29.24	29.24	-0.47	0.47	
					39	Maint	6.90	5.00	37.92	37.92	8.22	8.22	
					43	Rec	3.34	3.51	-4.68	4.68			
					57	Rec	2.36	1.72	37.47	37.47			
					78	Rec	0.74	0.89	-16.44	16.44			
20	WWF	8	26.7	20	5	Maint	8.83	8.00	10.34	10.34	5.74	5.74	0.70
					10	Maint	6.59	6.00	9.82	9.82	5.22	5.22	
					16	Maint	5.28	5.00	5.65	5.65	1.05	1.05	
					20	Maint	3.70	4.00	-7.44	7.44	-12.04	12.04	
					24	Rec	2.19	3.05	-28.10	28.10			
					28	Rec	1.38	2.46	-43.74	43.74			
					40	Rec	0.90	1.36	-33.54	33.54			
					46	Rec	0.83	1.10	-24.68	24.68			
					52	Rec	0.91	0.90	1.68	1.68			
					63	Rec	1.00	0.59	69.10	69.10			

Chapter 8: Comparison of anaesthesia and recovery of four anaesthetic techniques
Anaesthesia data (PP group)

Patient no	Age (yr)	Sex	Weight (kg)	Surgery	Induction dose (mg)	Propofol infusion (mg)	Total dose	Anaes quality	Pain	Apnoea	Involuntary movements	Anaes duration (min)
144	5	M	19.6	Circumcision	67.7	231.3	299	G	N	N	Y	29
138	4	M	16.3	Herniotomy	56.3	245.7	302	G	N	Y (20S)	N	40
137	6	M	24.5	Circumcision	84.7	185.3	270	Ad	Y	N	N	23
134	6	M	17.1	Circumcision	59.1	260.9	320	P	Y	Y (30S)	Y	23
136	6	M	19.4	Bil. HLPPV	67.0	309.0	376	Ad	Y	Y (40S)	Y	34
135	9	M	43.7	Circumcision	151.0	286.0	437	Ad	Y	Y (20S)	N	52
132	8	M	18.8	Herniotomy	65.0	278.0	343	P	N	Y (20S)	N	20
142	9	M	23.3	Circumcision	80.5	328.5	409	G	N	Y (15s)	N	33
151	9	M	39.0	Herniotomy	134.8	488.2	623	G	N	Y (45s)	N	41
150	6	M	23.6	Ex preauricularsinus	81.6	231.4	313	G	Y	N	N	24
128	9	M	29.7	Ex sebaceous cyst	102.6	316.4	419	G	N	Y(15S)	N	19
129	4	M	16.7	Circumcision	57.7	212.3	270	G	N	N	N	18
127	4	M	16.5	Herniotomy	57.0	165.0	222	Ad	N	Y(75S)	N	23
130	10	M	25.0	L orchidopexy	86.4	710.6	797	Ad	N	N	N	56
131	5	M	21.7	Herniotomy	75.0	273.0	348	G	N	Y(120S)	N	27
126	6	M	20.3	Circumcision	70.2	337.8	408	Ad	N	N	Y	26
152	8	M	26.7	Circumcision	92.3	224.7	317	G	N	N	N	20
124	9	F	33.0	Herniotomy	114.0	622.0	736	Ad	N	N	Y	47
141	10	M	27.0	Herniotomy	93.3	282.7	376	Ad	N	Y(60S)	N	25
158	7	M	20.2	Circumcision	69.8	202.2	272	P	N	Y (15S)	Y	22
162	5	M	18.4	Circumcision	63.6	266.4	330	Ad	N	Y(15S)	Y	25
133	5	M	18.8	Cir & herniotomy	65.0	472.0	537	G	N	N	N	36
165	4	M	12.8	Circumcision	44.2	175.8	220	P	N	N	Y	32.5
163	4	M	14.6	Circumcision	50.5	191.5	242	G	N	N	N	27
171	5	M	18.6	Herniotomy	64.3	215.7	280	Ad	Y	N	Y	41
168	6	M	22.7	Herniotomy	78.5	328.5	407	Ad	N	Y(20S)	Y	27
164	4	F	16.4	Herniotomy	56.7	313.3	370	Ad	Y	N	Y	43
170	10	M	22.9	Herniotomy	79.1	397.9	477	G	N	N	Y	38
169	9	F	36.4	Herniotomy	125.8	414.2	540	P	N	N	Y	36
166	5	M	23.7	Herniotomy	81.9	367.1	449	G	N	N	N	44
177	6	F	17.4	Herniotomy	60.1	146.9	207	G	N	N	N	16
159	10	M	24.3	Herniotomy	84.0	•	•	Ad	N	Y (10S)	N	19
167	9	M	22.4	Cystoscopy & biopsy	77.4	295.6	373	G	N	N	N	33
179	6	M	30.4	Cystoscopy	105.1	374.9	480	G	N	Y(60S)	N	42
180	8	M	24.0	Circumcision	82.9	316.1	399	G	N	N	N	34.4
182	6	M	31.1	Repair buried penis	107.5	383.5	491	•	N	Y(10S)	N	41
178	4	M	14.2	Ex cyst on penis	49.1	175.9	225	Ad	N	Y (15S)	N	18
181	8	M	30.1	Circumcision	104.0	433.0	537	G	N	N	N	35

Chapter 8: Comparison of anaesthesia and recovery of four anaesthetic techniques
Anaesthesia data (PH group)

Patient no	Age (yr)	Sex	Weight (kg)	Surgery	Induction dose (mg)	Propofol infusion (mg)	Total dose	Anaes quality	Pain	Apnoea	Involuntary movements	Anaes duration (min)
145	7	F	38.2	EUA cystoscopy	80.0	•	80	G	N	Y (5 S)	N	54
45	10	F	26.2	Accessory auride	80.0	•	80	Ad	N	N	N	26
47	10	M	30.7	Circumcision	90.0	•	90	Ad	N	N	Y	25
49	10	M	24.0	Meotoplasty	60.0	•	60	G	N	N	N	36
24	5	M	15.6	Herniotomy	55.0	•	55	Ad	N	Y (20S)	Y	41
29	11	M	29.5	Circumcision	105.0	•	105	G	N	N	Y	31
41	9	F	40.1	Herniotomy	90.0	•	90	G	N	Y (10S)	Y	45
148	8	M	25.5	R hydrocele	100.0	•	100	Ad	Y	N	Y	24
23	4	M	17.0	Herniotomy	60.0	•	60	Ad	Y	N	Y	35
100	7	F	20.1	Ex post auricula cyst	60.0	•	60	G	N	Y (15S)	N	19
65	10	M	24.0	Cystoscopy	126.0	•	126	Ad	N	N	Y	36
116	6	M	18.7	Herniotomy	50.0	•	50	G	N	N	Y	40
59	9	M	30.0	Circumcision	100.0	•	100	Ad	Y	N	Y	45
143	9	M	22.3	Herniotomy	66.0	•	66	Ad	Y	N	Y	31
149	7	M	27.4	Herniotomy	70.0	•	70	Ad	N	N	Y	33
101	9	M	30.0	Ex cyst glans penis	70.0	•	70	G	N	N	N	17
157	6	M	18.0	Cir & herniotomy	60.0	•	60	G	N	N	N	40
64	8	M	25.3	Circumcision	55.0	•	55	G	N	Y (20S)	Y	23
68	4	M	12.9	HLPPV	35.0	•	35	G	N	N	N	32
140	3	M	13.3	Circumcision	39.0	•	39	Ad	Y	Y(10S)	N	18
102	5	M	17.0	Cir & ureth dilatation	40.0	•	40	G	N	N	N	27
74	4	F	14.3	Ex alopecia	80.0	•	80	Ad	N	N	Y	19
69	4	M	15.7	Circumcision	50.0	•	50	G	N	N	N	44
35	4	M	15.0	Explo R groin mass	50.0	•	50	G	N	N	Y	21
87	10	M	31.0	Circumcision	70.0	•	70	Ad	Y	N	N	19
72	4	M	18.4	Herniotomy	55.0	•	55	G	N	Y (15S)	N	33
104	4	F	19.8	Excisional biopsy	60.0	•	60	G	N	N	Y	24
78	6	M	20.0	Circumcision	50.0	•	50	G	N	N	N	20
99	6	F	20.0	Ex L arm lump	40.0	•	40	G	N	N	N	26
77	4	M	12.4	Hydrococele	45.0	•	45	Ad	N	N	Y	39
32	11	F	33.4	Ex R thigh mass	65.0	•	65	G	N	N	N	30
109	5	M	17.5	Circumcision	60.0	•	60	Ad	N	N	Y	26
110	5	M	17.3	Circumcision	60.0	•	60	G	N	N	Y	23
175	5	M	16.8	Herniotomy	35.0	•	35	G	N	N	N	47
53	12	M	30.0	Herniotomy	80.0	•	80	G	N	Y(15S)	N	33
84	10	F	38.5	Ex DC upper lip	100.0	•	100	Ad	N	N	Y	23
81	8	F	18.7	Herniotomy	60.0	•	60	Ad	N	N	Y	41
91	7	M	23.2	Circumcision	42.0	•	42	Ad	N	N	N	26
174	10	M	29.0	Herniotomy	90.0	•	90	G	N	N	N	39
20	4	M	17.5	Circumcision	60.0	•	60	Ad	N	Y (20S)	N	32
173	4	M	14.9	HLPPV	40.0	•	40	G	N	N	N	50
176	10	M	55.6	Herniotomy	140.0	•	140	P	N	N	N	45

Chapter 8: Comparison of anaesthesia and recovery of four anaesthetic techniques
Anaesthesia data (TH group)

Patient no	Age (yr)	Sex	Weight (kg)	Surgery	Induction dose (mg)	Propofol infusion (mg)	Total dose	Anaes quality	Pain	Apnoea	Involuntary movements	Anaes duration (min)
62	10	M	24.3	Circumcision	125.0	•	125	Ad	N	N	N	23
73	4	M	13.1	Herniotomy	65.0	•	65	G	N	N	N	58
67	4	F	17.8	Ex lesion occiput	75.0	•	75	Ad	N	N	Y	25
114	5	F	12.2	Ex DC L thumb	50.0	•	50	G	N	N	N	45
70	4	M	15.4	Herniotomy	75.0	•	75	Ad	N	N	N	54
85	10	M	30.0	Circumcision	150.0	•	150	P	N	Y (15S)	Y	20
92	10	M	45.8	Ex L thigh nodule	200.0	•	200	G	N	N	N	8
108	4	M	16.8	Circumcision	85.0	•	85	Ad	N	N	Y	28
115	8	M	25.0	Herniotomy	125.0	•	125	Ad	N	Y (10S)	N	30
89	9	M	26.6	LIH & circumcision	125.0	•	125	G	N	N	N	38
154	7	M	29.0	Cir & L herniotomy	150.0	•	150	G	N	N	N	70
28	5	M	19.8	Herniotomy	90.0	•	90	G	N	Y (20S)	N	38
153	5	M	27.1	HLPPV	125.0	•	125	G	N	N	N	39
184	7	F	20.4	Herniotomy	100.0	•	100	G	N	N	N	40
156	7	M	21.4	Circumcision	100.0	•	100	G	N	Y (15S)	N	26
25	7	F	22.4	Removal FB L ear	90.0	•	90	G	N	N	N	5
26	11	M	34.0	L varicocele	136.0	•	136	G	N	N	N	47
146	5	M	19.8	Circumcision	90.0	•	90	P	N	Y (15S)	Y	16
55	8	M	14.0	Circumcision	56.0	•	56	Ad	N	N	N	55
98	9	M	27.1	Circumcision	150.0	•	150	G	N	N	N	42
39	6	M	16.8	Herniotomy	85.0	•	85	G	N	N	N	25
106	5	M	15.0	Herniotomy	75.0	•	75	G	N	N	N	20
111	9	M	25.3	Herniotomy	100.0	•	100	G	N	N	N	43
58	4	F	14.9	Herniotomy	50.0	•	50	G	N	N	N	28
46	9	M	28.8	LVDT & orchiopexy	125.0	•	125	G	N	N	Y	65
107	6	M	20.7	Circumcision	125.0	•	125	Ad	N	N	N	24
83	10	M	22.0	HLPPV	100.0	•	100	Ad	N	N	Y	18
119	4	M	18.2	Circumcision	90.0	•	90	G	N	N	N	28
96	9	M	27.3	Circumcision	125.0	•	125	G	N	N	N	26
75	8	M	21.1	Herniotomy	95.0	•	95	G	N	N	N	39
90	6	M	18.6	Circumcision	125.0	•	125	Ad	N	N	Y	33
60	7	F	19.0	Ex naevi thigh	85.0	•	85	G	N	N	N	15
122	5	M	17.5	Herniotomy	90.0	•	90	G	N	N	N	37
112	4	M	14.5	Circumcision	60.0	•	60	Ad	N	N	Y	28
44	6	M	17.1	HLPPV	80.0	•	80	Ad	N	Y (15S)	N	25
42	4	M	17.1	Herniotomy	75.0	•	75	Ad	N	N	Y	28
183	7	M	16.6	Circumcision	80.0	•	80	G	N	N	N	30
36	4	M	15.5	Herniotomy	75.0	•	75	G	N	Y(5S)	N	27
40	5	M	18.5	Herniotomy	60.0	•	60	Ad	N	N	N	30

Chapter 8: Comparison of anaesthesia and recovery of four anaesthetic techniques
Anaesthesia data (HH group)

Patient no	Age (yr)	Sex	Weight (kg)	Surgery	Induction dose (mg)	Propofol infusion (mg)	Total dose	Anaes quality	Pain	Apnoea	Involuntary movements	Anaes duration (min)
HH group												
57	8	F	28.0	Secondery suture	•	•	•	G	N	N	N	32
82	10	M	26.4	Circumcision	•	•	•	G	N	N	N	15
50	5	M	18.0	HLPPV	•	•	•	G	N	N	N	30
61	3	F	15.7	Ex coug naevi	•	•	•	G	N	N	N	53
79	8	F	32.0	Bil. herniotomy	•	•	•	G	N	N	N	31
63	11	F	31.2	Bil. herniotomy	•	•	•	G	N	N	N	54
16	6	M	20.9	Circumcision	•	•	•	Ad	N	N	N	45
66	5	F	18.5	Release trigger thumb	•	•	•	G	N	N	N	23
19	5	M	18.0	Circumcision	•	•	•	G	N	N	N	60
97	6	M	19.6	Circumcision	•	•	•	P	N	N	N	22
52	11	M	40.0	Circumcision	•	•	•	G	N	N	N	20
94	8	M	20.6	Circumcision	•	•	•	G	N	N	N	25
93	7	M	30.7	Circumcision	•	•	•	G	N	N	N	18
95	8	M	24.0	Circumcision	•	•	•	Ad	N	N	N	30
51	3	M	14.8	Circumcision	•	•	•	G	N	N	N	26
88	8	M	25.8	Circumcision	•	•	•	G	N	N	N	19
86	7	M	26.0	Orchidopexy	•	•	•	G	N	N	N	50
103	4	M	17.0	HLPPV	•	•	•	G	N	N	N	19
117	8	F	31.0	B.I.H.	•	•	•	G	N	N	N	65
121	3	M	15.2	HLPPV	•	•	•	G	N	N	N	60
123	7	F	18.0	B.I.H. repair	•	•	•	G	N	N	N	54
160	5	M	14.3	Circumcision	•	•	•	G	N	N	N	30
155	8	M	31.0	Circumcision	•	•	•	Ad	N	Y(20S)	N	22
118	4	M	16.3	R.I.H.	•	•	•	Ad	N	N	N	35
147	10	M	28.2	Circumcision	•	•	•	Ad	N	N	N	28
105	8	F	19.1	Ex periurethral wart	•	•	•	G	N	N	N	25
161	5	M	17.2	Circumcision	•	•	•	G	N	N	N	30
113	4	M	17.1	Release L trigg. thumb	•	•	•	G	N	N	N	28
125	4	M	14.5	Circumcision	•	•	•	G	N	N	N	20
120	4	M	15.1	Circumcision	•	•	•	Ad	N	N	N	32
34	5	M	18.0	Facial sebaceous cyst	•	•	•	G	N	N	N	27
48	8	M	33.0	Herniotomy	•	•	•	Ad	N	N	N	36
18	5	M	17.9	HLPPV	•	•	•	Ad	N	N	N	40
13	9	M	26.8	R.I.H.	•	•	•	G	N	N	N	27
30	11	M	29.0	Ex sebaceous cyst	•	•	•	G	N	N	N	30
21	5	M	27.9	Herniotomy	•	•	•	Ad	N	N	N	32
27	7	F	20.3	Bil. herniotomy	•	•	•	G	N	N	N	45
31	6	M	18.2	R varicocele	•	•	•	G	N	N	N	60
37	4	M	16.2	L herniotomy	•	•	•	G	N	N	N	34

Chapter 8: Comparison of anaesthesia and recovery of four anaesthetic techniques
Recovery data (PP group)

Patient no	Group	Time to full Steward score (min)	Time to open eye on command (min)	Time to orientation (min)	Psychomotor performance Baseline (min)	0.5 h postop (min)	1 h postop (min)	2h postop (min)
144	PP	40	40	40	22	•	•	29
138	PP	42	41	42	888	•	31	•
137	PP	15	15	16	16	48	30	15
134	PP	51	50	51	13	•	26	24
136	PP	45	40	45	10	•	25	20
135	PP	30	30	31	11	30	17	13
132	PP	70	60	70	18	•	•	35
142	PP	50	50	50	12	•	40	16
151	PP	27	27	27	8	50	25	19
150	PP	70	70	70	18	•	•	18
128	PP	50	50	50	13	•	55	16
129	PP	53	53	54	28	•	43	45
127	PP	44	41	44	30	•	50	26
130	PP	62	63	62	15	•	•	25
131	PP	55	55	60	22	•	60	28
126	PP	45	45	45	12	•	40	23
152	PP	40	46	46	18	•	26	21
124	PP	45	40	45	21	•	45	30
141	PP	46	45	•	15	•	20	22
158	PP	30	30	30	21	•	33	20
162	PP	43	39	45	22	•	35	29
133	PP	60	55	60	20	•	50	30
165	PP	28	26	28	75	80	45	60
163	PP	31	30	31	60	•	•	55
171	PP	35	35	37	18	•	36	39
168	PP	41	41	41	14	•	12	16
164	PP	45	50	48	27	•	25	30
170	PP	35	32	45	12	•	25	17
169	PP	22	17	22	13	40	15	8
166	PP	25	25	30	21	35	25	32
177	PP	37	37	37	25	•	26	21
159	PP	35	35	35	14	•	28	15
167	PP	19	19	19	14	42	22	16
179	PP	26	26	28	13	25	20	14
180	PP	30	30	30	12	35	15	16
182	PP	22	27	22	23	48	35	28
178	PP	52	52	52	45	•	40	47
181	PP	46	46	•	13	•	25	16

Chapter 8: Comparison of anaesthesia and recovery of four anaesthetic techniques
Recovery data (PH group)

Patient no	Group	Time to full Steward score (min)	Time to open eye on command (min)	Time to orientation (min)	Psychomotor performance Baseline (min)	0.5 h postop (min)	1 h postop (min)	2h postop (min)
145	PH	15	2	15	24	25	18	22
45	PH	12	10	14	11	20	22	17
47	PH	12	13	12	11	12	13	13
49	PH	15	25	15	13	28	20	17
24	PH	28	23	28	42	•	64	75
29	PH	11	11	11	13	24	11	16
41	PH	17	16	20	18	30	17	32
148	PH	17	17	18	19	21	15	17
23	PH	26	22	24.5	23	38	36	33
100	PH	25	25	25	20	20	29	20
65	PH	23	25	21	12	25	20	12
116	PH	15	15	15	20	20	20	18
59	PH	20	20	20	14	26	18	20
143	PH	32	32	32	15	24	17	21
149	PH	46	47	47	13	33	14.5	16
101	PH	18	18	18	13	20	18	14
157	PH	23	24	24	16	30	25	20
64	PH	20	20	20	17	25	28	28
68	PH	32	32	32	28	29	35	33
140	PH	38	39	40	75	•	79	58
102	PH	38	38	•	38	•	35	43
74	PH	26	23	26	33	75	36	30
69	PH	39	39	39	20	30	25	36
35	PH	34	29	34	27	•	39	37
87	PH	16	14	16	13	18	18	15
72	PH	45	45	•	25	•	36	40
104	PH	14	9	15	24	34	•	25
78	PH	22	22	22	20	23	27	23
99	PH	20	20	20	27	45	30	34
77	PH	22	22	22	38	45	40	40
32	PH	12	12	12	16	30	20	10
109	PH	15	15	15	25	30	20	25
110	PH	33	25	28	21	45	45	32
175	PH	19	19	27	20	36	25	19
53	PH	19	18	22	14	33	22	22
84	PH	19	18	19	12	25	20	22
81	PH	17	18	18	22	27	39	24
91	PH	15	15	15	14	25	18	20
174	PH	32	27	32	9	19	13	11
20	PH	29	28	29	26	42	30	54
173	PH	25	25	25	18	45	40	30
176	PH	5	5	5	13	22	19	21

Chapter 8: Comparison of anaesthesia and recovery of four anaesthetic techniques
Recovery data (TH group)

Patient no	Group	Time to full Steward score (min)	Time to open eye on command (min)	Time to orientation (min)	Psychomotor performance Baseline (min)	0.5 h postop (min)	1 h postop (min)	2h postop (min)
62	TH	16	16	17	13	18	17	14
73	TH	25	25	25	40	•	50	45
67	TH	8	8	8	20	25	25	22
114	TH	16	13	16	26	26	41	32
70	TH	31	31	31	41	•	35	58
85	TH	25	25	25	11	15	12	9
92	TH	12	12	12	9	10	9	11
108	TH	15	15	15	51	75	45	36
115	TH	20	20	20	17	40	20	18
89	TH	12	10	12	13	25	24	22
154	TH	13	13	13	17	26	40	29
28	TH	32	32	32	23	•	26	31
153	TH	20	20	20	16	29	29	23
184	TH	19	19	19	24	49	24	32
156	TH	30	29	30	16	20	15	15
25	TH	18	18	18	20	40	25	18
26	TH	25	25	25	12	50	17	•
146	TH	49	46	49	29	•	25	36
55	TH	•	•	•	15	•	39	18
98	TH	15	15	15	21	25	20	25
39	TH	11	9	17	18	30	26	28
106	TH	25	25	25	21	27	37	29
111	TH	16	30	20	15	20	21	22
58	TH	21	21	21	35	•	•	•
46	TH	24	24	24	14	22	15	18
107	TH	25	15	25	18	52	26	25
83	TH	22	17	22	13	26	25	18
119	TH	50	50	50	22	•	34	43
96	TH	46	46	46	12	•	31	19
75	TH	30	30	32	18	35	20	15
90	TH	48	48	48	20	•	33	25
60	TH	35	40	35	25	•	28	20
122	TH	12	11	12	31	65	55	58
112	TH	15	15	17	18	42	25	•
44	TH	34	36	40	22	•	34	29
42	TH	30	28	31	45	70	48	40
183	TH	21	21	21	21	40	38	45
36	TH	16	16	39	27	48	26	26
40	TH	20	17	22	35	59	45	40

Chapter 8: Comparison of anaesthesia and recovery of four anaesthetic techniques
Recovery data (HH group)

Patient no	Group	Time to full Steward score (min)	Time to open eye on command (min)	Time to orientation (min)	Psychomotor performance Baseline (min)	0.5 h postop (min)	1 h postop (min)	2h postop (min)
57	HH	11	10	13	14	40	25	24
82	HH	21	21	21	10	•	15	23
50	HH	35	35	35	25	•	45	•
61	HH	24	24	25	45	•	42	48
79	HH	12	11	12	15	20	15	•
63	HH	13	12	13	13	•	18	34
16	HH	16	16	16	21	30	45	40
66	HH	16	10	20	17	32	44	22
19	HH	25	25	27	37	44	36	42
97	HH	17	17	17	19	23	22	25
52	HH	17	17	17	12	17	19	17
94	HH	15	15	15	18	21	24	20
93	HH	29	29	29	15	27	16	18
95	HH	16	29	16	17	20	22	19
51	HH	23	23	23	62	•	•	•
88	HH	22	21	21	16	20	17	18
86	HH	30	30	30	18	39	22	20
103	HH	15	15	16	42	50	54	34
117	HH	7	7	7	15	25	22	30
121	HH	28	28	38	38	95	56	50
123	HH	22	22	22	15	13	30	26
160	HH	4	3	4	30	35	40	39
155	HH	30	30	30	11	18	20	16
118	HH	23	21	23	38	49	44	34
147	HH	41	41	41	17	19	19	14.5
105	HH	14	14	14	15	25	15	44
161	HH	16	13	16	20	32	31	23
113	HH	12	12	12	22	28	27	25
125	HH	28	28	29	33	40	36	32
120	HH	11	10	11	31	25	25	41
34	HH	24	22	25	20	•	•	23
48	HH	21	21	21	13	30	21	26
18	HH	26	25	60	36.5	•	53	57
13	HH	13	11	13	21	26	•	22
30	HH	10	5	10	12	25	32	16
21	HH	24	22	24	21	•	20	35
27	HH	23	23	23	22	•	32	16
31	HH	23	30	•	22	60	53	38
37	HH	17	35	41	21	40	42	44

APPENDIX D

Personal Work

PERSONAL WORK

It is certified that all the work of this thesis was personally undertaken by Cindy ST Aun, apart from the following:-

1. Assistance and guidance with the statistics were given by Dr. DHY Leung. Many of the statistical calculations were performed by the Centre for Clinical Trials and the Computer Centre of the Chinese University of Hong Kong.

2. All the propofol and protein binding assays were performed by Miss Perpetua Tan.

3. The analysis of α_1 acid glycoprotein and albumin concentrations were performed by Dr. M. Arumanayagam.

4. The computer programs for pharmacokinetic model infusion pump was written by Mr. YH Tam. Least squares regression on the infusion data was performed by Mr YH Tam.

5. Assistance with the pharmacokinetic program was given by Dr. TA Lim.

6. The echocardiographic recordings and measurements were performed by Dr. Rita YT Sung.

APPENDIX E

Ethical Committee Approval Certificate

FACULTY OF MEDICINE
THE CHINESE UNIVERSITY OF HONG KONG
香港中文大學
醫學院

TIN · NT · HONG KONG · ~~TEL.: 0-6352111~~ · TELEGRAM · SINOVERSITY · TELEX · 50301 CUHK HX · 香港新界沙田 · 電話：~~六三五二~~

~~Reference~~: Dean : Prof. T.E. Oh MB BS DA FFARCS FFARACS FFARACS (IC) Tel. 695 2870
Planning Officer : Mr. Andrew Chan BA CertEdMgt Tel. 695 2850

TELEGRAM . SINOVERSITY
TELEX . 50301 CUHK HX
FAX : (852) 695 0958

Our Ref: FM/C/13

25 August 1989

Dr. Cindy S.T. Aun
Department of Anaesthesia & Int. Care
Prince of Wales Hospital
CUHK

Dear Dr. Aun,

I write to inform you that covering approval has been given for you to engage in the projects entitled:

1. "Propofol in Paediatrics – Induction Dose Finding Study"
(Investigators include: Drs. Cindy S.T. Aun, Stephen M. Short and John K.L. Lew)

2. "Propofol Pharmacokinetics in Children"
(Investigators include: Drs. Cindy S.T. Aun, Stephen M. Short and John K.L. Lew)

Yours sincerely,

Andrew Chan
Secretary
Ethical Sub-Committee

AC/bc

FACULTY OF MEDICINE
THE CHINESE UNIVERSITY OF HONG KONG
香港中文大學
醫學院

TIN · NT · HONG KONG · TEL.: 0-6352111 · TELEGRAM · SINOVERSITY · TELEX · 50301 CUHK HX · 香港新界沙田 · 電話：零一六三五二

Reference: Dean : Prof. T.E. Oh MB BS DA FFARCS FFARACS FFARACS (IC) Tel. 695 2870
Planning Officer : Mr. Andrew Chan BA CertEdMgt Tel. 695 2850

TELEGRAM . SINOVERSITY
TELEX . 50301 CUHK HX
FAX : (852) 603 6958

Our Ref: FM/C/13

12 September 1991

Dr. Cindy S.T. Aun
Department of Anaesthesia & Int. Care
Prince of Wales Hospital
CUHK

Dear Dr. Aun,

I write to inform you that covering approval has been given for you to engage in the projects entitled:

1. "Comparison of the Cardiovascular Responses using Thiopentone or Propofol for Induction of Anaesthesia in Children"
(Investigators include: Drs. C.S.T. Aun, T. Short, M. O'Meara, R. Sung and Prof. T.E.Oh)

2. "Postoperative Oxygen Saturation in Patients with Cleft Lip and Palate"
(Investigators include: Drs. C.S.T. Aun, T. short, Y.H. Tam, K. Liu and Prof. T.E. Oh)

Yours sincerely,

Andrew Chan
Secretary
Ethical Sub-Committee

AC/bc

HE CHINESE UNIVERSITY
F HONG KONG
ACULTY OF MEDICINE
HATIN. NT. HONG KONG

香港中文大學
醫學院
香港新界沙田

TELEGRAM · SINOVERSITY TELEX · 50301 CUHK HX FAX: (852) 603 6958

ur Reference : FM/C/13
our Reference :

1 February 1994

Dr. C.S.T. Aun
Department of Anaesthesia & Intensive Care
CUHK

Dear Dr. Aun,

I write to inform you that approval has been given for you to engage in the project entitled "Recovery characteristics following Propofol infusion in children" in according with the protocol submitted. It has been noted that investigators for the study are your good self, Dr. M. O'Meara, Dr. T.G. Short and Mrs. Y.M. Rowbottom, Dept. of Anaesthesia & Intensive Care, CUHK.

Please submit a copy of the consent form to be signed by the subjects, which should preferably be in Chinese, if not in both Chinese and English, for record.

Yours sincerely,

Andrew Chan
Secretary
Clinical Research Ethics Committee

AC/bc